Physiol Rev
82: 637–672, 2002; 10.1152/physrev.00004.2002.

Modification of Brain Aging and Neurodegenerative Disorders by Genes, Diet, and Behavior

MARK P. MATTSON, SIC L. CHAN, AND WENZHEN DUAN

Laboratory of Neurosciences, National Institute on Aging Gerontology Research Center, Baltimore, Maryland

I. Introduction 637
II. Adaptive Cellular and Molecular Responses in Brain Aging 641
A. Neuroprotective mechanisms 641
B. Neurorestorative mechanisms 642
III. Genetic Factors in Brain Aging and Neurodegenerative Disorders 644
A. Genes that influence life span and brain health span 644
B. Genes that cause or increase risk of neurodegenerative disorders 644
IV. Dietary Factors in Brain Aging and Neurodegenerative Disorders 651
A. Effects of dietary restriction on brain aging: neuroplasticity and neuroprotection 651
B. Cellular and molecular mechanisms underlying the neural effects of dietary restriction 652
C. Folic acid 655
D. Antioxidants 657
V. Behavioral Modification of Brain Aging 658
A. Intellectual activity 659
B. Exercise 659
VI. Synapses and Aging: Emerging Concepts 660
VII. Implications for Prevention and Treatment of Neurodegenerative Disorders 660

Mattson, Mark P., Sic L. Chan, and Wenzhen Duan. Modification of Brain Aging and Neurodegenerative Disorders by Genes, Diet, and Behavior. *Physiol Rev* 82: 637–672, 2002; 10.1152/physrev.00004.2002.—Multiple molecular, cellular, structural, and functional changes occur in the brain during aging. Neural cells may respond to these changes adaptively, or they may succumb to neurodegenerative cascades that result in disorders such as Alzheimer's and Parkinson's diseases. Multiple mechanisms are employed to maintain the integrity of nerve cell circuits and to facilitate responses to environmental demands and promote recovery of function after injury. The mechanisms include production of neurotrophic factors and cytokines, expression of various cell survival-promoting proteins (e.g., protein chaperones, antioxidant enzymes, Bcl-2 and inhibitor of apoptosis proteins), preservation of genomic integrity by telomerase and DNA repair proteins, and mobilization of neural stem cells to replace damaged neurons and glia. The aging process challenges such neuroprotective and neurorestorative mechanisms. Genetic and environmental factors superimposed upon the aging process can determine whether brain aging is successful or unsuccessful. Mutations in genes that cause inherited forms of Alzheimer's disease (amyloid precursor protein and presenilins), Parkinson's disease (α-synuclein and Parkin), and trinucleotide repeat disorders (huntingtin, androgen receptor, ataxin, and others) overwhelm endogenous neuroprotective mechanisms; other genes, such as those encoding apolipoprotein E_4, have more subtle effects on brain aging. On the other hand, neuroprotective mechanisms can be bolstered by dietary (caloric restriction and folate and antioxidant supplementation) and behavioral (intellectual and physical activities) modifications. At the cellular and molecular levels, successful brain aging can be facilitated by activating a hormesis response in which neurons increase production of neurotrophic factors and stress proteins. Neural stem cells that reside in the adult brain are also responsive to environmental demands and appear capable of replacing lost or dysfunctional neurons and glial cells, perhaps even in the aging brain. The recent application of modern methods of molecular and cellular biology to the problem of brain aging is revealing a remarkable capacity within brain cells for adaptation to aging and resistance to disease.

I. INTRODUCTION

Many persons live for nine or more decades and enjoy a well-functioning brain until the very end of life. We therefore know what the brain is capable of and, accordingly, a major goal of research in the area of the neurobiology of aging is to identify ways to facilitate successful brain aging in everyone. Studies of brains of the oldest old have provided evidence for stability as well as plasticity in successful brain aging (Fig. 1). In many

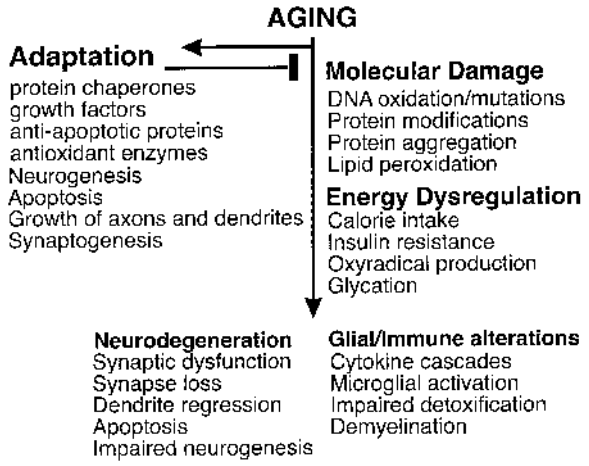

FIG. 1. During aging there is a progressive accumulation of damaged molecules and impaired energy metabolism in brain cells. Neurons and glial cells may adapt to the adversities of aging by increasing their ability to cope with stress, compensating for lost or damaged cells by producing new neurons and glia, and remodeling neuronal circuits. If adaptation is not successful, then molecular damage to neurons and inflammatory processes result in synaptic dysfunction and neuronal degeneration and death.

brain regions, there is very little or no decrease in numbers of neurons, while in some brain regions neuronal loss may occur but may be compensated by expansion of dendritic arbors and increased synaptogenesis in the remaining neurons (19). It is thought that many neurons remain in the brain for a lifetime, although in some brain regions such as the olfactory bulb and dentate gyrus of the hippocampus, there may be a continuous replacement of neurons from a pool of progenitor (stem) cells (91, 291). This regenerative capacity of some brain regions may persist throughout life. Changes in the cellular structure of the brain and the functions of its neuronal circuits are controlled by an intricate array of intercellular signaling molecules and intracellular signal transduction pathways. Several such cellular signal transduction systems are altered during brain aging. Examples of widely used signaling mechanisms affected by aging include protein phosphorylation (alterations in kinases and phosphatases) (150), cellular calcium homeostasis (215), and gene transcription (180). Among neurotransmitter systems, dopaminergic signaling appears to be consistently altered during aging with a progressive decrease in signaling via the D2 subtype of receptor (303). In addition to signaling pathways, cellular systems that regulate protein folding (chaperone proteins) and degradation (proteasomal and lysosomal systems) are altered in brain cells during aging (158) (Fig. 2). These kinds of alterations that occur during normal aging may set the stage for catastrophic neurodegenerative disorders that may be triggered by particular genetic predispositions or environmental factors, while other age-related changes may represent adaptive protective responses to the aging process.

Studies of embryonic and early postnatal development, and of synaptic plasticity in the young adult, have made a major contribution to our current understanding of the molecular and cellular mechanisms that determine whether brain aging occurs successfully or manifests dysfunction or disease. This is because the same intercellular signals and intracellular transduction pathways that regulate neurite outgrowth, synaptogenesis, and cell survival during development are also operative throughout life (213). Although new signaling systems continue to be discovered, the major classes of signaling molecules important in brain aging include neurotrophic factors, neurotransmitters, cytokines, and steroids. Neurotrophic factors such as neurotrophins [brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotensin (NT)-3, and NT-4], fibroblast growth factors, glial-derived neurotrophic factor (GDNF), and ciliary neurotrophic factor (CNTF) have been shown to promote the survival of specific populations of brain neurons under experimental conditions relevant to brain aging and neurodegenerative disorders (232). In addition to their roles as mediators of synaptic transmission, neurotransmitters such as glutamate, acetylcholine, and dopamine also play important roles in regulating the formation of neuronal circuits during development and in influencing the neurodegenerative process in brain disorders of aging (215). Sex steroids (estrogen and testosterone) and stress steroids (glucocorticoids) have been shown to have quite striking effects on brain function and structure, and alterations in regulation of their production and signaling mechanisms have been reported to occur during aging (239). The status of such neurotransmitter, trophic factor, cytokine, and steroid hormone signaling systems is likely to have a major influence on the outcome of brain aging.

While the brain can age successfully, its cells may face considerable adversity during the journey (Fig. 1). Increased oxidative stress (oxyradical production) and accumulation of oxidatively damaged molecules (proteins, nucleic acids, and lipids) promote dysfunction of various metabolic and signaling pathways (178). Neurons may also face energy deficits as the result of alterations in the cerebral vasculature and in mitochondrial function (131). As in other organ systems, cells in the brain encounter a cumulative burden of oxidative and metabolic stress that may be a universal feature of the aging process. Each of the major classes of cellular molecules, including proteins, nucleic acids, and lipids, is oxidatively modified during brain aging. Protein modifications include carbonyl formation (34, 35, 74); covalent modification of cysteine, lysine, and histidine residues by the lipid peroxidation product 4-hydroxynonenal (261, 268, 266); nitration on tyrosine residues (326); and glycation (249). DNA and RNA bases are subject to oxidative modification, with a prominent example being the formation of 8-hydroxydeoxyguanosine (331). Double bonds in mem-

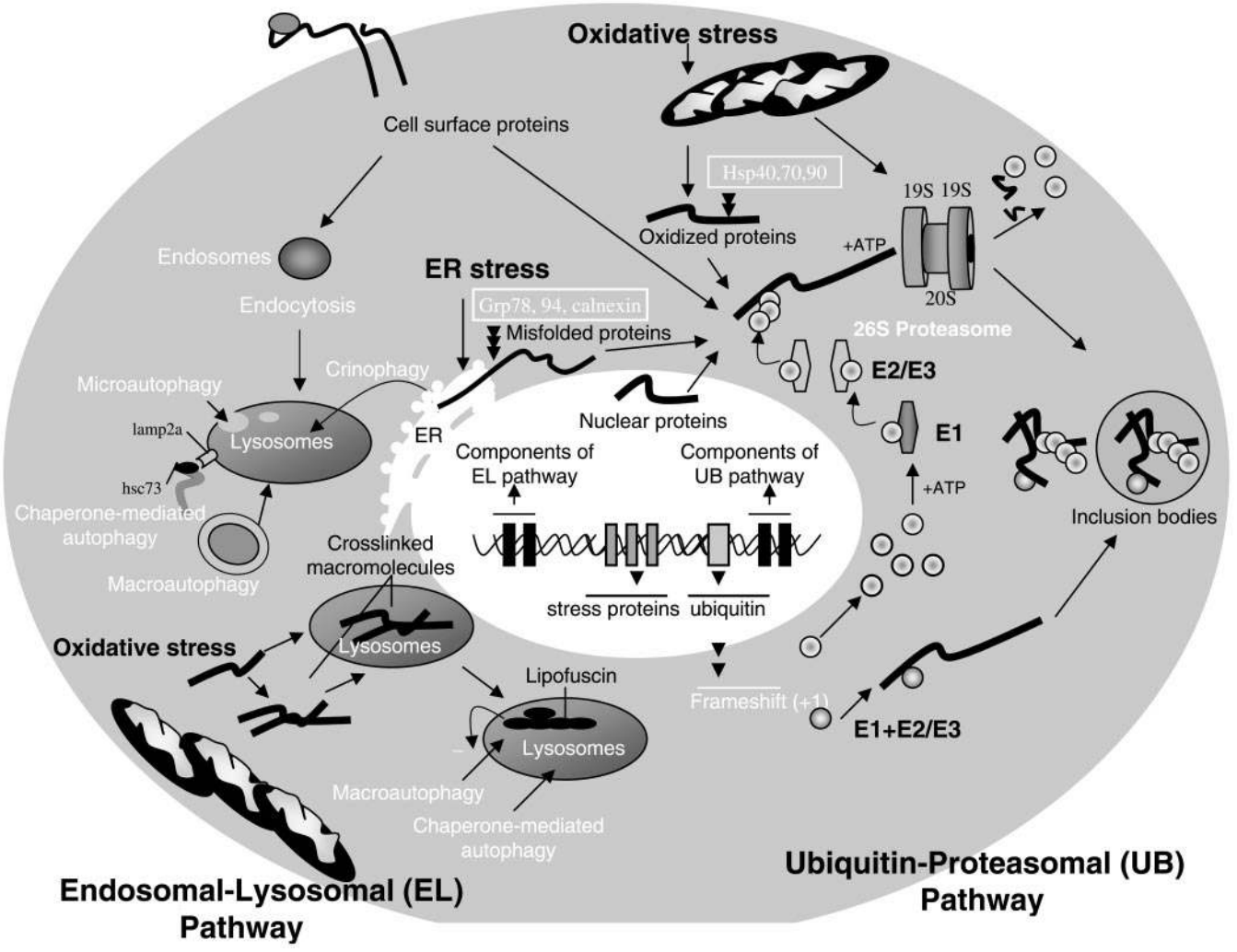

FIG. 2. Mechanisms involved in regulating protein turnover and their modification by cellular stress. Proteins damaged by oxidative stress or other modifications can be degraded by the proteasomal or lysosomal systems. Protein chaperones such as heat shock proteins (HSP40, HSP70, and HSP90), glucose-regulated proteins (GRP78 and GRP94), and ubiquitin play important roles in controlling protein folding and targeting proteins for proteolytic degradation. ER, endoplasmic reticulum.

brane lipids are oxidized resulting in the production of a variety of lipid peroxides and aldehydes (218). These modifications of proteins, nucleic acids, and lipids are greatly exacerbated in neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) consistent with a major role for oxidative stress of aging in the pathogenesis of those disorders (207).

Analyses of experimental animal and cell culture models of age-related neurodegenerative disorders have provided insight into the mechanisms that result in increased oxidative stress and damage to proteins, nucleic acids, and membrane lipids (Fig. 3). The pathogenesis of AD involves altered proteolytic processing of the β-amyloid precursor protein (APP) resulting in increased production of a long (42 amino acid) form of amyloid β-peptide which self-aggregates and forms insoluble plaques in the brain (216). As amyloid β-peptide aggregates, it generates reactive oxygen species that can induce membrane lipid peroxidation in neurons resulting in the impairment of the function of membrane ion-motive ATPases and glucose transporter proteins, which, in turn, disrupts cellular ion homeostasis and energy metabolism (216). These oxidative actions of amyloid β-peptide can cause dysfunction of synapses and may render neurons vulnerable to excitotoxicity and apoptosis (80, 219). In PD, degeneration of dopaminergic neurons in the substantia nigra may be triggered by mitochondrial impairment and increased oxidative stress resulting from aging and exacerbated by environmental factors (147). In the common late-onset forms of AD and PD, the neurodegenerative cascade is most likely promoted by environmental factors (see sects. IV and V) that result in increased oxidative and metabolic

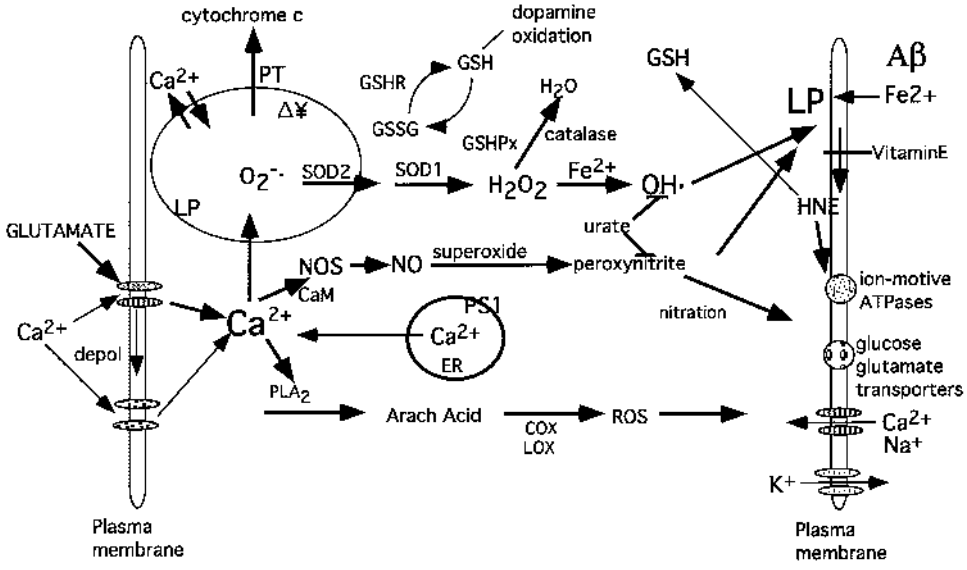

FIG. 3. Examples of sources of oxidative stress in neurons during aging and examples of molecules damaged by free radical-mediated processes. A major source of oxyradicals is mitochondria, in which superoxide anion radical ($O_2^-\cdot$) is produced during oxidative phosphorylation. Superoxide is converted to hydrogen peroxide (H_2O_2) via the actions of mitochondrial manganese superoxide dismutase (Mn-SOD) and cytosolic Cu/Zn-SOD. Hydrogen peroxide is eliminated from cells by conversion to water in reactions catalyzed by catalase and glutathione peroxidases. However, hydrogen peroxide is an important source of hydroxyl radical (OH·) which is generated in the Fenton reaction which involves Fe^{2+} or Cu^{2+}. Hydroxyl radical is a potent inducer of membrane lipid peroxidation. Oxyradicals can also be generated in response to calcium influx via the activation of nitric oxide (NO) synthase, resulting in NO production; NO can interact with superoxide to produce peroxynitrite. In addition, various oxygenases can be activated by calcium resulting in superoxide production. Oxyradicals (particularly hydroxyl, superoxide, and peroxynitrite) can damage proteins, lipids, and nucleic acids. Lipid peroxidation products such as 4-hydroxynonenal (HNE) can covalently modify proteins and impair their function. Arach acid, arachidonic acid; CaM, calmodulin; depol, depolarization; ER, endoplasmic reticulum; GSH, glutathione; GSHPx, glutathione peroxidase; GSHR, glutathione reductase; GSSG, reduced glutathione; LP, lipid peroxidation; PLA_2, phospholipase A_2; NOS, NO synthase; PS1, presenilin-1; PT, permeability transition pore; SOD1, Cu/Zn-superoxide dismutase; SOD2, manganese superoxide dismutase.

stress. On the other hand, more rare inherited forms of these disorders in which disease onset occurs at an early age (30–60 years of age) are caused by specific mutations; for example, mutations in APP and presenilins that cause AD (122) and mutations in α-synuclein and parkin that cause PD (165, 281). Some neurodegenerative disorders are purely genetic including Huntington's disease (HD) and related trinucleotide repeat disorders (389); such disorders may not, therefore, be considered as diseases of aging, although aging processes may affect the age of disease onset and clinical course.

In the United States and other industrialized countries, life expectancy continues to increase, and therefore, more people will suffer from age-related neurodegenerative conditions. The negative impact of age-related neurodegenerative disorders on our societies is emphasized by the fact that more dollars are required to care for patients with AD, PD, and stroke than are spent on the combined care for patients with cardiovascular disease or cancer. Each neurodegenerative disorder is characterized by dysfunction and degeneration of specific populations of neurons in the brain (246). Neurons in brain regions involved in learning and memory processes, such as the hippocampus and cerebral cortex, are afflicted in AD. In PD, dopaminergic neurons in the substantia nigra degenerate resulting in motor dysfunction (147). A stroke occurs when a cerebral blood vessel becomes occluded or ruptures resulting in the degeneration of neurons in the brain tissue supplied by that vessel (65). Several genetic and environmental factors that may initiate the neurodegenerative process in AD, PD, and stroke have been identified, and this information has led to the development of valuable animal models of these disorders. Animal models of AD include transgenic mice overexpressing mutant forms of human APP (93, 133), transgenic and knockin mice expressing mutant forms of human presenilin-1 (PS1) (75, 108), and infusion of amyloid β-peptide and excitotoxins into the brains of rats and mice (31, 97). Animal models of PD include administration of the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to monkeys and mice resulting in selective degeneration of substantia nigra dopamine-producing neurons and associated motor dysfunction (71), and transgenic mice expressing mutant human α-synuclein which exhibit degeneration of dopaminergic neurons and a behavioral phenotype with features similar to PD (210). Stroke models involve transient or permanent occlusion of the middle cerebral artery in rats and mice (65, 378). The mecha-

nisms that result in neuronal dysfunction and/or death in these models are beginning to be understood, with increased oxidative stress, perturbed energy metabolism, altered calcium homeostasis, and activation of apoptotic cascades playing important roles in most cases (219). Data obtained using these various models have provided valuable insight into the cellular molecular mechansims of neurodegenerative disorders and will therefore be cited throughout the remainder of this article.

II. ADAPTIVE CELLULAR AND MOLECULAR RESPONSES IN BRAIN AGING

A goal of basic and clinical neuroscientists is to identify approaches for promoting the maintenance of cognitive, emotional, motor, and sensory functions throughout the life span.

This could be accomplished by avoiding genetic (through genetic counseling or germline gene therapy, for example) and environmental (dietary and behavioral factors, for example) factors that facilitate neuronal dysfunction and death, or by enhancing the ability of neurons to adapt to the aging process. Basic research is identifying cellular signaling mechanisms that promote cell survival, neurite growth, and/or synapse formation/plasticity; understanding these signaling pathways may reveal ways of promoting successful brain aging. Clinicians, geneticists, and epidemiologists should therefore work together to identify genetic and environmental factors that cause or affect risk of age-related neurological disorders.

A. Neuroprotective Mechanisms

Intercellular signaling mechanisms mediate the second-to-second functions of neuronal circuits as well as long-term changes in the biochemistry and structure of those circuits. Three major classes of intercellular signaling proteins that regulate neuronal survival and synaptic plasticity are neurotransmitters, neurotrophic factors, and hormones. Glutamate and GABA, the major excitatory and inhibitory neurotransmitters in the brain, play pivotal roles in regulating neuronal survival (231) and synaptic plasticity (18). By inducing the expression of neurotrophic factors such as BDNF, glutamate can promote neuronal survival (203). On the other hand, overactivation of glutamate receptors can cause neuronal death, particularly under conditions of increased levels of oxidative and metabolic stress, as occurs during aging and in age-related neurodegenerative disorders (224). By reducing neuronal excitability, GABA can protect neurons in experimental models of neurodegenerative disorders (231). Other neurotransmitters that can modify neuronal vulnerability in cell culture and animal models of neurodegenerative disorders include acetylcholine, dopamine, norepinephrine, and serotonin (89, 214, 288). During brain aging, these neurotransmitters may contribute to either degeneration or adaptive responses of neurons.

Neurotrophic factors promote the survival, outgrowth, and/or synaptogenesis of neurons. Examples of neurotrophic factors that have been shown to counteract untoward aspects of aging (oxidative stress and disturbed ion homeostasis, for example) include basic fibroblast growth factor (bFGF), NGF, BDNF, NT-4, transforming growth factor-β (TGF-β), tumor necrosis factor (TNF), and GDNF. These neurotrophic factors can protect one or more populations of brain neurons against excitotoxic, oxidative, and metabolic insults in models of stroke, AD, PD, and HD (232, 233). Signaling by cell adhesion proteins such as integrins may also play important roles in modulating neuronal survival (94). Growth factors, cytokines, and integrin ligands promote neuronal survival by inducing the expression of genes that encode proteins that suppress oxidative stress, stabilize cellular calcium homeostasis, and antagonize neurodegenerative biochemical cascades. Examples of three neuroprotective signaling cascades, activated by BDNF, bFGF, and the secreted form of APP are shown in Figure 4. bFGF, BDNF, TNF, and NGF can increase the production of one or more antioxidant enzymes [Cu/Zn-superoxide dismutase (SOD), Mn-SOD, glutathione peroxidase, and catalase] in hippocampal neurons (233, 229). NGF, BDNF, and TNF can induce expression of anti-apoptotic Bcl-2 family members (32) and inhibitor of apoptosis proteins (IAP) (364). Neurotrophic factors can also modulate the expression and/or activity of subunits of glutamate receptors and voltage-dependent calcium channels in ways that promote neuronal survival and synaptic plasticity (217, 225, 360). Kinases such as mitogen-activated protein (MAP) kinase and protein kinase C, and transcription factors such as NF-κB and CREB, transduce the cell survival signals of neurotrophic factors and cytokines.

Another type of adaptive response that may protect neurons against the adversities of aging and disease is a stress response that involves protein chaperones that exhibit neuroprotective properties. Examples of such stress proteins include heat shock proteins (e.g., HSP-70, HSP-90, and HSP-60) and glucose-regulated proteins (e.g., GRP-78 and GRP-94). These chaperone proteins interact with many different proteins in cells and function to ensure their proper folding, on the one hand, and degradation of damaged proteins, on the other hand (86, 96). They may also interact with, and modify the function of, apoptotic proteins including caspases (14, 293). Levels of some of these chaperone proteins may be increased during aging as a protective response (180, 182). Cell culture and in vivo studies have shown that HSP-70 and GRP-78 can protect neurons against injury and death in experimental models of neurodegenerative disorders (197, 380). Interestingly, caloric restriction, a dietary manipulation

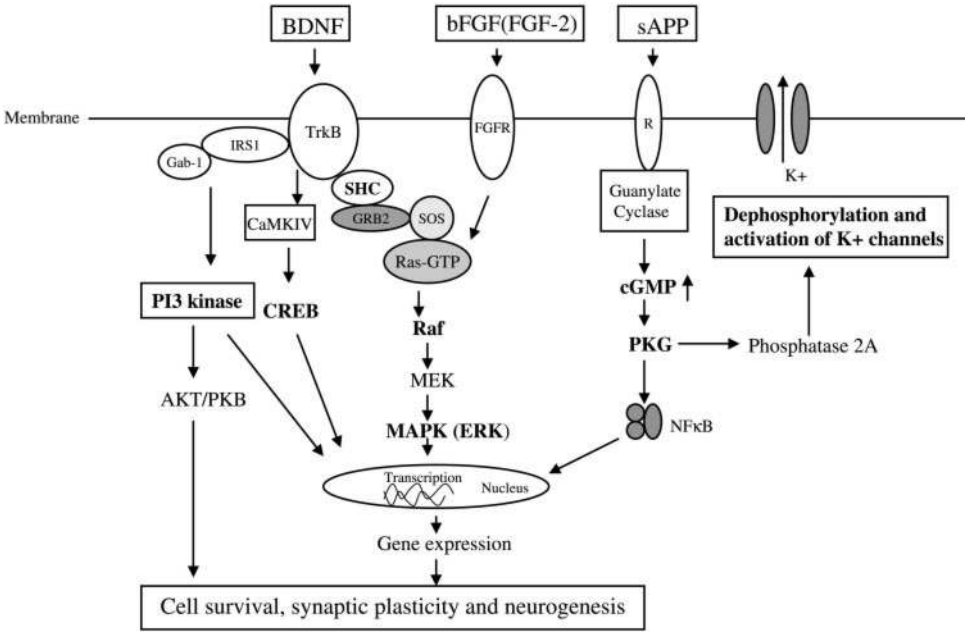

FIG. 4. Examples of cellular signaling pathways that modulate neuronal plasticity and survival during aging. Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) activate membrane receptor tyrosine kinases that initiate kinase signaling cascades that ultimately regulate the expression of genes that encode proteins which enhance neuronal survival and plasticity. Such gene targets include those encoding proteins that suppress apoptotic cascades, reduce oxidative stress, and stabilize cellular calcium homeostasis. AKT/PKB, Akt kinase; CaMKIV, calcium/calmodulin-dependent protein kinase IV; CREB, cAMP response element binding protein; IRS1, insulin receptor substrate-1; MAPK, mitogen-activated protein kinase; MEK, MAP kinase kinase; PI3K, phosphatidylinositol 3-kinase; PKG, protein kinase G; R, receptor; sAPP, secreted form of amyloid precursor protein; SHC, src homology domain-containing adaptor protein; trkB, high-affinity BDNF receptor.

that increases life span and brain "health span" (the time window of life during which the brain maintains a level of function that permits a productive life-style), can increase the expression of chaperone proteins in the brains of rats and mice (see sect. IV).

Synapses are sites where the actions of neurotrophic factors, stress proteins, and anti-apoptotic Bcl-2 and IAP family members may play particularly important roles in preserving the integrity and function of neuronal circuits (115, 228). The impact of aging is likely to be most severe in synapses, because these compartments are sites of repetitive calcium influx and oxyradical production; it is therefore of great importance to understand how genes and environment affect synaptic homeostasis (see sect. VI).

B. Neurorestorative Mechanisms

Research performed in many different laboratories during the past 10 years has revealed that regeneration/compensation can occur in the adult brain and that populations of stem cells or neural progenitor cells (NPC) may play a role in this process by dividing and then differentiating into neurons or glia (91). Various neurotrophic factors and cytokines may promote neurogenesis, neurite outgrowth, and synaptic recovery after brain injury (146, 232). Damage to axons and dendrites can result in regrowth of those processes; however, in contrast to the peripheral nervous system, the brain contains a number of inhibitory signals that may prevent successful reinnervation of target cells (312). If synaptogenesis does occur, it may or may not replace lost function depending on the degree of specificity of neuronal connections in the circuits involved. For example, reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement (333). On the other hand, many brain functions rely on "memories" based on the past history of synaptic activity, and such memories are unlikely to be restored by new synapse formation.

Stem cell biology is a rapidly growing area in the fields of neuroscience research and aging. Embryonic stem cells have received considerable attention because of their ability to form any type of cell in the body including neurons (99). They are therefore a potential cell source for replacement of neurons lost in neurodegenerative disorders. Two major populations of pluripotent NPC are present in the adult brain, one in the subventricular zone and the other in the subgranular layer of the dentate gyrus of the hippocampus (91). These NPC cells can give rise to either neurons or astrocytes, and there is increasing evidence that some of the progeny of the NPC survive and become functional, although many may undergo programmed cell death (Fig. 5). Newly generated cells in the brain can be identified by giving animals the thymidine analog bromodeoxyuridine (BrdU); the phenotype of their differentiated progeny can then be determined by double-labeling using antibodies against neuronal (e.g., neural cell adhesion molecule or β_3-tubulin) or astrocyte [glial fibrillary acidic protein (GFAP)] markers. Several signals that control the proliferation, differentiation, and survival of NPC have been identified (91, 291). bFGF and epidermal growth factor (EGF) can maintain NPC in a proliferative state, whereas BDNF and NT-3 can promote their

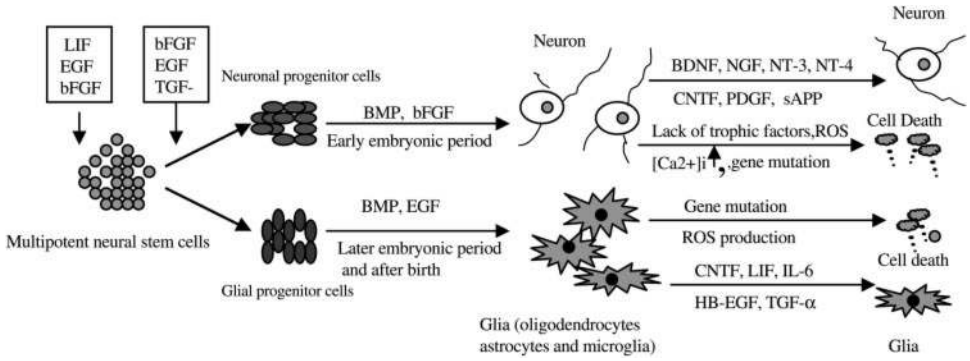

FIG. 5. Regulation of neurogenesis and gliogenesis. Neural stem cells capable of producing neurons and astrocytes are maintained in a self-replicating state by cytokines and neurotrophic factors such as leukemia inhibitory factor (LIF) and epidermal growth factor (EGF). Under the appropriate conditions, the stem cells can form neuron- or glia-restricted progenitor cells which, in turn, can cease dividing and differentiate into neurons or glia. New neurons may integrate into neuronal circuits or may die, and glia may also live or die. BDNF, brain-derived neurotrophic factor; bFGF, basic fibroblast growth factor; BMP, bone morphogenic protein; CNTF, ciliary neurotrophic factor; HB-EGF, heparin-binding epidermal growth factor; IL-6, interleukin-6; NGF, nerve growth factor; NT-3, neurotrophin-3; NT-4, neurotrophin-4; TGF-α, transforming growth factor-α; PDGF, platelet-derived growth factor; ROS, reactive oxygen species; sAPP, secreted form of amyloid precursor protein.

differentiation and/or survival, and bone morphogenetic protein can induce NPC to become astrocytes (91, 241). Additional signals that control NPC cell fate include Notch (344), Numb (40), neurogenin (339), and the secreted form of APP (255). Brain injury is a potent stimulus for neurogenesis (194), and this effect is likely mediated by the trophic factors and cytokines induced by cell injury (232).

Considerable interest in fundamental mechanisms of cellular aging has arisen from studies of telomerase, a reverse transcriptase that adds a six-base DNA repeat onto the ends of chromosomes (telomeres) and thereby maintains their integrity during successive rounds of cell division (221). Expression of the catalytic subunit of telomerase (TERT) and telomerase activity are associated with cell immortalization and cancer and are absent from most somatic cells in the adult, suggesting an important role in the aging process. Indeed, expression of TERT in normal fibroblasts makes them immortal (without transforming them) (24). Telomerase is present in brain cells during development, where it is thought to play a role in the maintenance of NPC in a proliferative state, and in promoting survival of NPC and their neuronal and glial progeny (87, 166). Telomerase is also present in NPC in the adult brain where its expression may be influenced by brain injury and other environmental factors. Recent studies suggest that TERT expression can be induced by BDNF and sAPPα (W. Fu and M. P. Mattson, unpublished data). It has been reported that TERT can prevent apoptosis of cultured neurons in experimental models relevant to AD and stroke (87, 387), suggesting that if TERT expression could be induced in neurons or NPC in the adult brain, it may increase the resistance of neurons to age-related neurodegenerative disorders (221). DNA damage may trigger neuronal death in age-related neurodegenerative processes, and telomerase may suppress such DNA damage responses (198); nuclear localization and reverse transcriptase activity appear to be critical for the antiapoptotic function of TERT (P. Zhang and M. P. Mattson, unpublished data).

The possibility that the aging process impairs neurogenesis is suggested by studies in which BrdU-labeled cells were quantified in the brains of middle-aged and old rats (174). This adverse effect of aging on neurogenesis may be counteracted by many of the same environmental conditions that promote successful brain aging. Indeed, dietary restriction can increase neurogenesis (183). Interestingly, neurogenesis can also be increased by environmental enrichment (164, 254) and physical exercise (351). Because no specific molecular markers of NPC have been established, and because NPC cannot be labeled by the usual BrdU method in clinical studies of humans, it is not known whether abnormalities in neurogenesis contribute to the pathogenesis of age-related neurodegenerative disorders. However, recent studies of experimental models of AD have shown that amyloid β-peptide can impair neurogenesis (124). Both the proliferation and survival of NPC in the dentate gyrus of the hippocampus are reduced in APP mutant mice. Infusion of amyloid β-peptide into the lateral ventricle of adult mice impairs neurogenesis of NPC in the subventricular region. Moreover, exposure of cultured human NPC to amyloid β-peptide impairs their proliferation and differentiation and can induce apoptosis (124). These experimental findings suggest that adverse effects of amyloid β-peptide on NPC may contribute to depletion of neurons and cognitive impairment in AD. Although it is not known whether a failure of neurogenesis contributes to the pathogenesis of PD, several studies in rodents, nonhuman primates, and humans suggest that functional recovery can occur after transplantation of

NPC or mobilization of endogenous NPC (21, 323). The development of methods for identifying NPC and their recent progeny in post mortem brain tissue sections from human patients would greatly facilitate our understanding of the relative contributions of neuronal degeneration and impaired neurogenesis to neurodegenerative disorders.

The implications of neurogenesis for facilitating successful brain aging and treating age-related neurodegenerative disorders are quite profound. It may be possible to mobilize endogenous NPC in the brain or to introduce exogenous NPC to replace dysfunctional or dead neurons and glia. As described above, three different behavioral modifications have been shown to enhance neurogenesis (dietary restriction and increased intellectual and physical activities). In addition, pharmacological approaches for mobilizing NPC are being developed. For example, it has been shown that antidepressant drugs such as serotonin transport inhibitors can increase production of BDNF and stimulate neurogenesis (5, 201). There have already been reports of improved functional outcome following NPC transplantation in models of traumatic central nervous system injury (238), demyelinating disorders (372), and PD (21). Particularly intriguing are reports suggesting that stem cells in other organs of the body, including bone marrow, are capable of forming neurons and glial cells (242). A major clinical hurdle in interindividual transplantations is immune attack on the transplanted cells; this could be avoided by using a person's own stem cells for transplantation. Embryonic stem cells may also prove valuable in treating various neurodegenerative disorders because of their multipotent properties and their reduced reactivity toward immune cells.

III. GENETIC FACTORS IN BRAIN AGING AND NEURODEGENERATIVE DISORDERS

The probability of living a long life with preservation of a high level of brain function is strongly influenced by the genes one inherits. Accordingly, genetic factors also play important roles in determining one's risk of age-related neurodegenerative disorders. In this section we review the evidence for the involvement of specific genes in the determination of life span and risk of neurological disorders of aging.

A. Genes That Influence Life Span and Brain Health Span

There is ample evidence that life span (52, 193, 274), intelligence (57, 240), and risk of various neurological disorders (51, 337, 355) are determined, in part, by heritable factors. However, the specific genes involved and their mechanisms of action are largely unknown. One gene that appears to have an influence on aging in general, and on risk of age-related neurodegenerative disorders, is apolipoprotein E (327). Three alleles of apolipoprotein E encode proteins that differ in two amino acids; E2 contains a cysteine in each position, E3 contains a cysteine in one of the positions, and E4 does not contain a cysteine in either position. Individuals with an E4 allele have a reduced life span (126) and are at increased risk of AD (157). The mechanism whereby E4 may accelerate brain aging has been suggested to involve a decreased antioxidant and neuroprotective properties of this isoform (Fig. 6). The cysteine residues in E2 and E3 may bind to and thereby detoxify 4-hydroxynonenal, a cytotoxic product of lipid peroxidation (266).

Other genes linked to life span that may influence brain aging are those encoding growth hormone (10) and major histocompatability complex (MHC) proteins (36). Growth hormone levels decrease with aging, and this change is ameliorated by caloric restriction. The density of microvessels in the brains of rodents decreases during aging, and this can be reversed by treating the animals with growth hormone, which may increase production of insulin-like growth factor I (IGF-I) in the brain (332). The latter studies further showed that IGF-I can reverse age-related impairment in learning and memory. IGF-I can also protect neurons against injury and death in experimental models of AD and related neurodegenerative disorders (46, 386). MHC genes are expressed in neurons (58). Mice that are genetically deficient for class I MHC proteins exhibit incomplete synaptogenesis in the developing visual system and enhanced long-term potentiation of synaptic transmission in the hippocampus (135), suggesting important roles for MHC proteins in learning and memory.

Inherited variability of mitochondrial genes encoding proteins involved in oxidative phosphorylation and other aspects of mitochondrial function may also contribute to aging (60) and the pathogenesis of neurodegenerative disorders (258). Mitochondrial DNA damage has been shown to increase in brain cells during aging (121), and it has been proposed that accumulation of mitochondrial DNA mutations is a major factor in the aging process itself (260).

B. Genes That Cause or Increase Risk of Neurodegenerative Disorders

The past decade has been filled with major advances in our understanding of the pathogenesis of age-related neurodegenerative disorders, as the result of the combined efforts of molecular geneticists and cell and molecular biologists. More that 20 different genes have been identified in which mutations cause an inherited form of a neurodegenerative disorder. Once such a gene is discovered, the pathogenic mechanism of the mutated form of

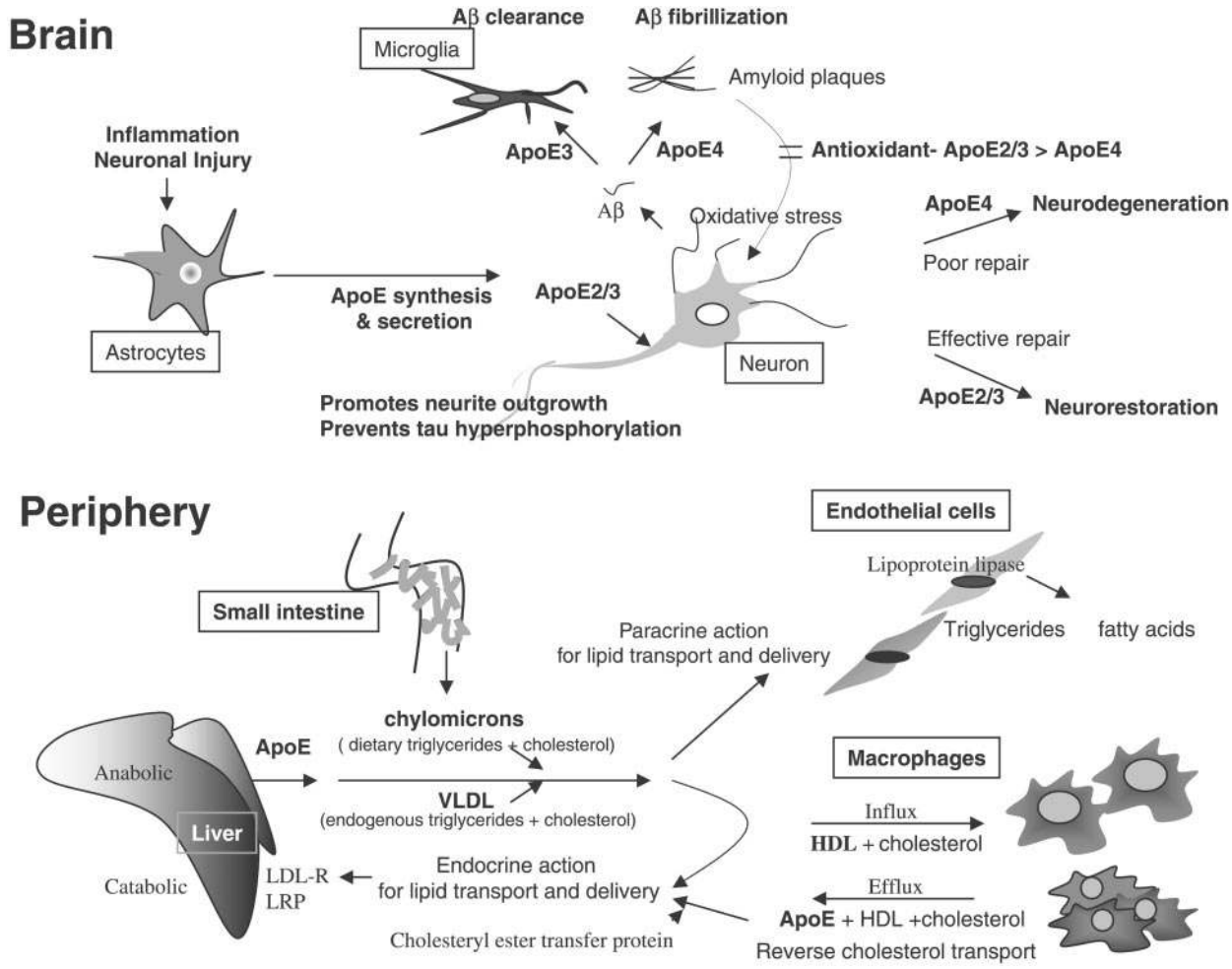

FIG. 6. Possible mechanisms of action of different apolipoprotein E isoforms in promoting or preventing age-related pathological changes in the brain and periphery. In the brain, apolipoprotein E is produced mainly by astrocytes. Apolipoprotein E can promote neuronal survival and outgrowth and may play important roles in adaptive responses to aging and brain injury. The beneficial effects of apolipoprotein E may involve an antioxidant function. The E2 and E3 isoforms are more effective than the E4 isoform in their antioxidant and biological activities. Mechanisms of apolipoprotein production and metabolism in the periphery are shown in the *bottom panel*. Individuals with the E4 isoform are prone to atherosclerosis, which may be due to a diminished antioxidant activity of this isoform resulting in enhanced damage to vascular endothelial cells.

the gene can be elucidated in studies of cultured cells and transgenic mice expressing the mutant gene. In this section we describe how the discovery of such disease-causing genes has revealed why neurons become dysfunctional and die in several of the most prominent neurodegenerative disorders including AD, PD, HD, and amyotrophic lateral sclerosis (ALS). What emerges from the studies described below is a view of neurodegenerative disorders in which genetic compromise renders the brain vulnerable to the aging process, with specific populations of neurons being disproportionately affected. In general, disease-causing mutations appear to act mainly by accelerating the same neurodegenerative cascade that occurs in more common sporadic forms of the disease.

Although the vast majority of cases of AD are sporadic with no clear pattern of inheritance and a late age of onset (70s and 80s), some cases are inherited in an autosomal dominant manner with complete penetrance and an early age of onset (40s and 50s). The first gene linked to familial AD is located on chromosome 21 and encodes the APP, the source of the 40- to 42-amino acid amyloid β-peptide (Aβ) that forms insoluble amyloid plaques in the brains of all AD patients (122). Several different disease-causing mutations in APP have been reported, all of which are located within or adjacent to the Aβ sequence, and all of which increase production of Aβ-(1—42). The most intensely studied APP mutations are the "Swedish" mutation (a 2-amino acid substitution adjacent to the NH_2 terminus of Aβ; Ref. 177) and the "London" mutation (a missense mutation adjacent to the COOH terminus of Aβ; Ref. 42). In addition, several AD kindreds have been identified in which mutations within the Aβ sequence are

pathogenic (253). Two other genes linked to early-onset familial AD are those encoding PS1 (chromosome 14) and PS2 (chromosome 1); more than 70 different PS1 mutations (all except one are missense mutations), and 2 PS6 mutations have been reported (122). PS1 and PS2 are structurally similar integral membrane proteins with eight transmembrane domains and are localized mainly in the endoplasmic reticulum (ER). The presenilin-1 mutations tend to cluster in the cytoplasmic loop region and in or near transmembrane domain 2. The identification of the mutations in the APP and presenilin genes has led directly to experiments that have revealed, at least in part, how they cause AD (Fig. 7; Ref. 226).

A well-documented abnormality that results from APP mutations, as well as presenilin mutations, is increased production of Aβ [particularly Aβ-(1—42)] and decreased production of sAPPα (6, 122, 216). Aβ can impair synaptic function and can render neurons vulnerable to excitotoxicity and apoptosis by the following mechanism. During the process of self-aggregation, Aβ generates reactive oxygen species (hydrogen peroxide and hydroxyl radical) by a mechanism that may involve metal-catalyzed oxidation of methionine (128, 134, 353). When this process occurs in the immediate vicinity of cell membranes, lipid peroxidation is initiated (204, 205). In neurons, Aβ-induced lipid peroxidation impairs the function of ion-motive ATPases (sodium and calcium pump proteins), glucose transporter proteins (204–206), and GTP-binding proteins (163). Aβ can also induce oxidative stress in astrocytes resulting in impaired glutamate trans-

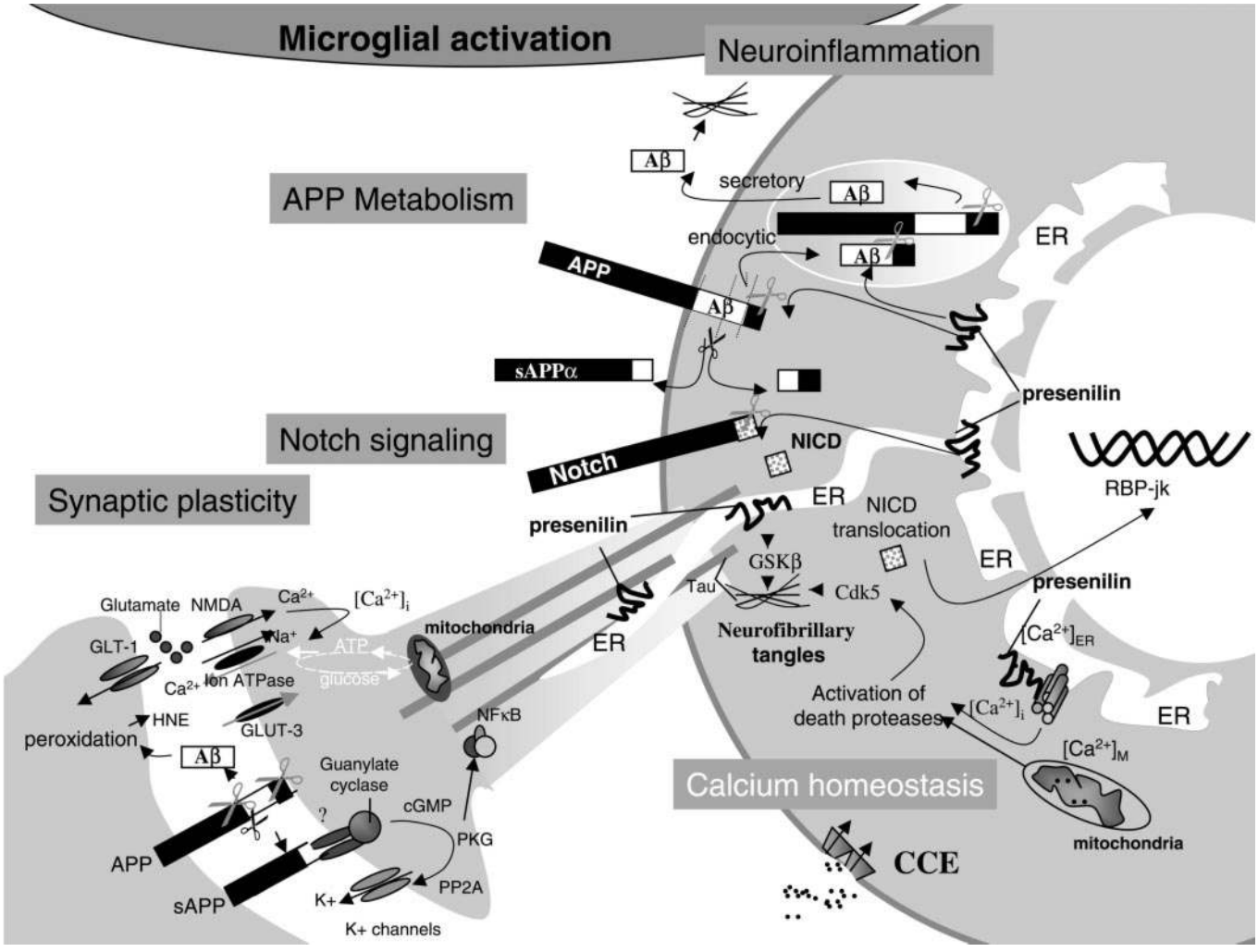

FIG. 7. Mechanisms underlying the pathogenic actions of mutations in amyloid precursor protein (APP) and presenilins. Mutations in APP, as well as presenilin mutations, shift the proteolytic processing of APP such that more Aβ is produced and less sAPPα is produced. Presenilins play an essential role in γ-secretase cleavage of APP and may also facilitate Notch cleavage and release of the transcription-regulating Notch COOH-terminal domain (NICD). Presenilin mutations have a major impact on endoplasmic reticulum (ER) calcium signaling, effectively increasing the pools of ryanodine- and inositol trisphosphate-sensitive stores. The normal functions of APP and presenilins, and the consequences of Alzheimer's disease-linked mutations in these proteins, may be particularly important in synapses.

port (23). By this mechanism, Aβ disrupts neurotransmitter signaling, destabilizes cellular calcium homeostasis, and renders neurons vulnerable to excitotoxicity and apoptosis (204, 227). Oxidative stress induced by Aβ may be particularly detrimental for neuronal function and survival when it occurs in synapses (162).

Exposure of cultured neurons to Aβ can trigger programmed cell death which manifests characteristic mitochondrial membrane alterations and release of cytochrome *c* and caspase activation. Aβ stimulates the production of apoptotic proteins including Par-4, Bax, and the tumor suppressor protein p53 (55, 80, 109, 111, 262). Analyses of post mortem brain tissue from AD patients reveals evidence for neuronal apoptosis including upregulation of Par-4 (109) and caspase activation (38). Agents that stabilize mitochondrial function and caspase inhibitors protect neurons against Aβ-induced death (109, 111, 234).

In addition to increasing production of Aβ, APP and presenilin mutations decrease the production of sAPPα (6). A decrease in sAPPα levels may contribute to the pathogenesis of AD, because sAPPα normally functions in modulating synaptic plasticity (learning and memory) and in promoting survival of neurons (90, 142, 230). The mechanism whereby sAPPα promotes neuronal survival and synaptic plasticity involves activation of potassium channels and of the transcription factor NF-κB; these actions of sAPPα stabilize cellular Ca^{2+} homeostasis and suppress oxyradical production (225).

AD patients typically exhibit emotional disturbances and abnormal stress responses involving increased glucocorticoid production that likely result from pathological changes in brain regions that control such behaviors and stress responses including limbic structures such as the amygdala and hippocampus and the frontal cortex (300). Studies of APP mutant transgenic mice suggest that such abnormal stress responses are the result of increased levels of Aβ in these brain regions. APP mutant mice exhibit an age-dependent increase in sensitivity to physiological stressors, which is associated with abnormalities in hypothalamic-pituitary-adrenal function and dysregulation of blood glucose levels (267). Two related neuropeptides that may play a role in the alterations in affective behaviors in AD patients and APP mutant mice are corticotropin-releasing hormone (CRH) and urocortin. CRH is expressed in brain regions prone to degeneration in AD, and CRH can protect cultured hippocampal and cortical neurons against cell death caused by Aβ (271). Urocortin and urocortin II are CRH-related neuropeptides that act on CRH receptors expressed by neurons in the hippocampus and functionally related brain regions. Urocortin can protect hippocampal neurons against excitotoxic and oxidative injury by activating the type I CRH receptor and a signaling pathway involving cAMP-dependent protein kinase, protein kinase C, and MAP kinase (272). These findings suggest roles for CRH and urocortin in antagonizing the neurodegenerative process in AD. It remains to be determined whether pharmacological manipulations of CRH/urocortin signaling will benefit AD patients.

Two major consequences of presenilin mutations are perturbed cellular calcium homeostasis (226) and altered APP processing (122) (Fig. 6). At this point in time, it remains unclear which defect is a primary consequence of the mutations and which is secondary. PS1 and PS2 mutations increase the vulnerability of cultured cells to apoptosis and excitotoxicity (108, 110, 112, 367). Hippocampal neurons in PS1 mutant knockin mice are more vulnerable to excitotoxicity and apoptosis (108). Perturbed calcium regulation in the ER is central to the cell death-promoting effects of PS1 mutations (Fig. 7). The abnormality involves an increased pool of ER calcium resulting in increased calcium responses when cells are challenged with glutamate or agonists that stimulate calcium release from the ER (39). Abnormal ER calcium signaling caused by presenilin mutations may promote altered capacitative calcium influx through voltage-dependent channels in the plasma membrane (186, 375). Presenilin mutations result in altered APP processing, and there is evidence that presenilins are critical for γ-secretase activity (369) and Notch cleavage (63). Altered APP processing may not account for the spectrum of effects of PS mutations. Instead, altered APP and Notch processing caused by PS mutations may result from altered calcium-mediated regulation of the enzyme activities that mediate cleavage of the two proteins (191, 276, 284, 316, 361). Indeed, one or more secretase activities are sensitive to calcium (44). Notch signaling may promote neuronal survival by enhancing cellular calcium homeostasis, an action antagonized by a protein called Numb; alterations in Notch and Numb functions may play roles in the pathogenesis of AD (40).

Mutations in genes encoding the proteins α-synuclein and Parkin can cause early-onset familial PD; α-synuclein mutations are inherited in an autosomal dominant manner, while mutations in parkin are inherited in an autosomal recessive manner (280). The α-synuclein gene is located on chromosome 4, and the Parkin gene is located on chromosome 6. α-Synuclein is a vesicle-associated protein, and Parkin is a cytoplasmic protein. α-Synuclein is axonally transported and associates with vesicles in presynaptic terminals, suggesting a role in regulation of vesicle trafficking (148). Parkin is expressed primarily in neurons where it is localized at particularly high levels in neurites (137). Studies of the pathogenic actions of three missense mutations in α-synuclein (A53T, A30P, and G209A) have provided new insight into the events that lead to the dysfunction and degeneration of dopaminergic neurons in PD (Fig. 8). Expression of α-synuclein mutations in cultured cells increases their vulnerability to ox-

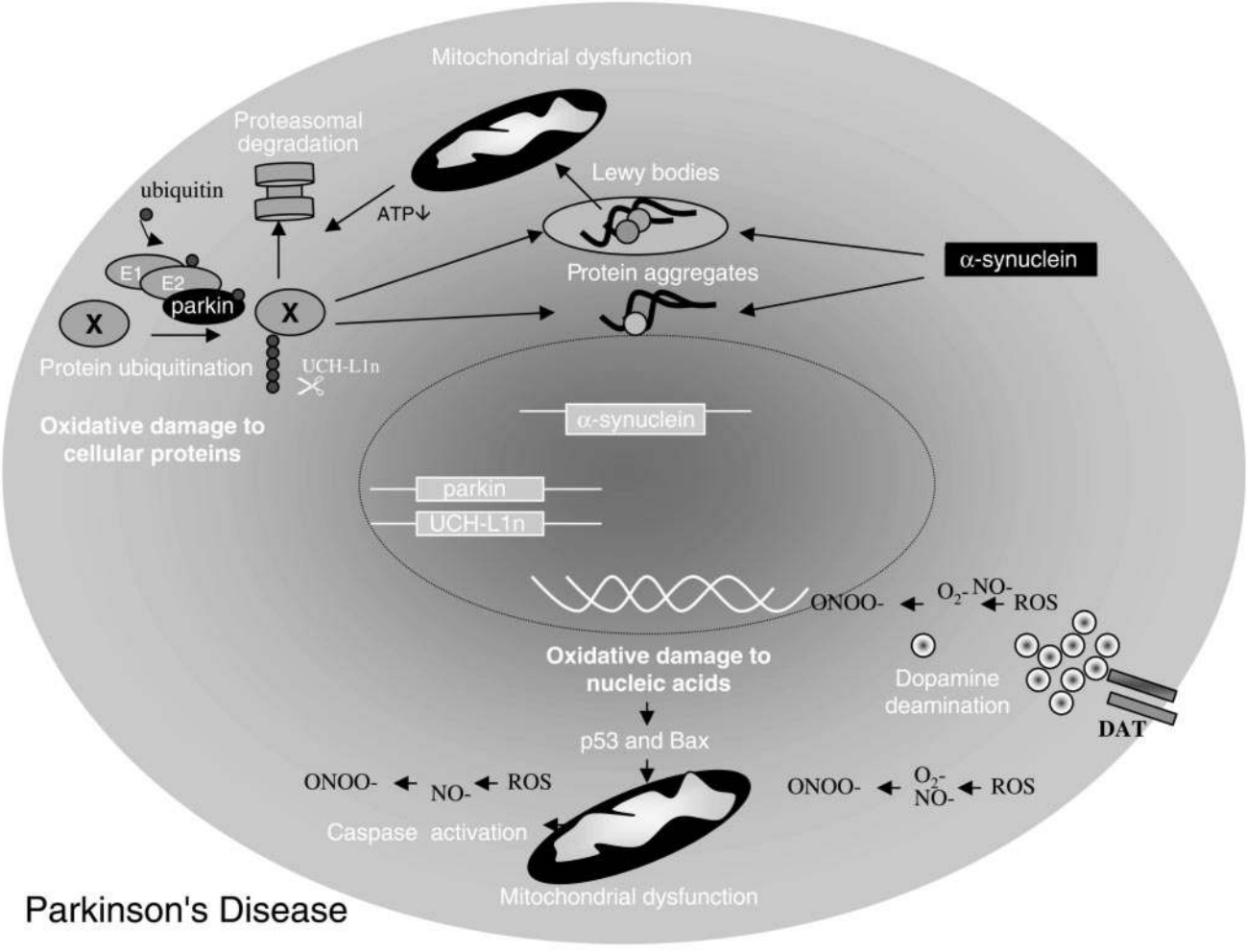

FIG. 8. Mechanisms of neuronal degeneration in familial Parkinson's disease (PD). In sporadic PD, alterations in dopamine metabolism and/or exposure to environmental toxins such as MPTP and rotenone can induce oxidative stress in dopaminergic neurons resulting in their dysfunction and death. Familial PD can be caused by mutations in α-synuclein or Parkin. Mutations in α-synuclein may cause excessive protein aggregation that triggers apoptosis and/or impair presynaptic function. Parkin mutations may interfere with protein degradation by the proteasome. In both sporadic and familial PD, dopaminergic neurons are subjected to increased oxidative stress that may trigger apoptosis.

idative stress and apoptosis (342). Overexpression of wild-type or mutant α-synuclein induces apoptosis in cultured neurons (305); PC12 cells overexpressing mutant α-synuclein exhibit decreased proteasome activity and increased vulnerability to mitochondrial dysfunction and apoptosis (343). Masliah et al. (210) reported evidence for loss of dopaminergic neurons and Lewy body-like cytoplasmic inclusions in α-synuclein mutant mice. However, another line of mice expressing mutant α-synuclein driven by a tyrosine hydroxylase promoter did not exhibit pathology in the substantia nigra (211). α-Synuclein forms aggregates that may exhibit toxic properties similar to those of Aβ including production of reactive oxygen species (347) and increased membrane ion permeability (357). Collectively, these findings suggest that α-synuclein mutations may promote neuronal degeneration by causing abnormalities in protein degradation and oxidative stress. Some data point to a loss of function, as opposed to a gain of function in the pathogenic action of α-synclein mutations. Thus α-synuclein knockout mice exhibit a defect in dopamine release (1), and overexpression of wild-type (but not mutant) α-synuclein protects cultured neural cells against apoptosis (56).

Parkin is a ubiquitin-protein ligase that presumably functions in protein degradation; Parkin mutations result in loss of the ubiquitin-protein ligase activity (320). It was recently reported that parkin can ubiquitinate α-synuclein (321), suggesting a link between impaired proteasomal degradation of α-synuclein and the neurodegenerative process. These observations strongly suggest that a defect in protein degradation is central to the pathogenesis of PD and further suggest strong mechanistic interactions between oxidative stress and protein degradation in neurodegenerative disorders in general, since oxidative damage

to proteins often makes them targets for ubiquitination and proteasomal degradation. In addition to disease-causing mutations, risk of PD may be influenced by genetic polymorphisms, a possibility that is currently being investigated by several laboratories (43, 356).

The genetics of HD are seemingly straightforward; all cases of this disease are believed to be caused by the expansion of trinucleotide (CAG) repeats in the huntingtin gene (located on chromosome 4) resulting in long stretches of polyglutamine repeats in the huntingtin protein (76, 199). However, the consquences of the huntingtin mutation may be subject to modification by aging, as suggested by evidence for variability in age of disease onset and progression of the clinical phenotype. HD patients manifest progressive motor dysfunction characterized by involuntary body movements due to degeneration of neurons in the basal ganglia, principally the caudate and putamen (3). As the disease progresses, the neurodegenerative process may spread to regions of the cerebral cortex, thalamus, and cerebellum resulting in cognitive dysfunction and emotional disturbances. Recently, a closely related familial HD-like disorder was described that appears to result from a trinucleotide expansion in a yet-to-be identified gene (202).

The alterations caused by polyglutamine expansions in huntingtin that result in neuronal death are beginning to be revealed (Fig. 9). Overexpression of mutant human huntingtin in cultured cells and transgenic mice can induce spontaneous cell death (apoptosis) and can increase the vulnerability of neurons to excitotoxicity (130, 192, 294, 346). Several different behavioral abnormalities have been described in mice expressing mutant huntingtin including motor deficits and cognitive dysfunction (250, 311). The reason that trinucleotide expansions in huntingtin promote degeneration of striatal neurons in HD is unclear. Mutant huntingtin self-aggregates resulting in the

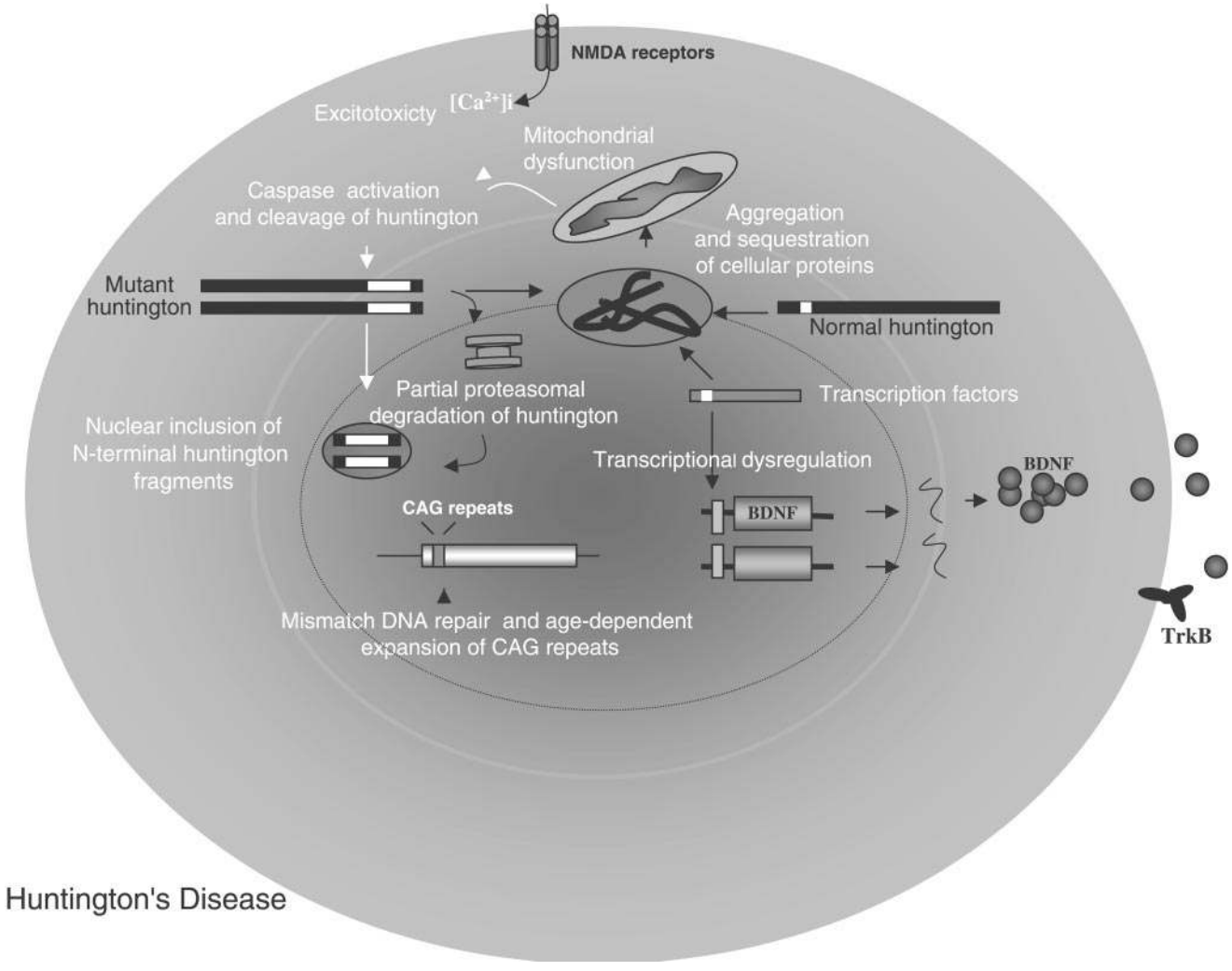

FIG. 9. Pathogenic mechanisms of mutant huntingtin. Huntington's disease is caused by polyglutamine expansions in the huntingtin protein. Mutant huntingtin may self-aggregate and trigger activation of caspases. Data also suggest that mutant huntingtin can cause a depletion of BDNF production by suppressing transcriptional activity.

formation of inclusions in the nucleus and cytoplasm (120, 311). Neurons in mice expressing mutant huntingtin exhibit increased caspase activation, and administration of caspase inhibitors to the mice can suppress the neurodegenerative process (257), suggesting that mutant huntingtin triggers programmed cell death. Cells expressing mutant huntingtin exhibit altered proteasomal function that may trigger apoptosis (145). Mutant huntingtin may trigger apoptosis by weakening the interaction of huntingtin with huntingtin interacting protein-1 (Hip-1), thereby allowing Hip-1 to interact with a protein called Hippi that then recruits caspase-8 and thereby initiates the cell death cascade (223).

Interestingly, adverse effects of mutant huntingtin on cell function are not limited to the nervous system because abnormalities in adipocytes have been described that may be related to the well-known alterations in energy metabolism in HD patients (82). The ability of dietary supplementation with creatine to delay motor symptoms and increase survival in huntingtin mutant mice (7) is consistent with impaired cellular energy metabolism in the neurodegenerative process. Finally, it was recently reported that levels of BDNF are decreased in HD (390), suggesting that decreased neurotrophic support may be a consequence of huntingtin mutations that promotes the degeneration of striatal neurons.

In each of the three neurodegenerative disorders just described (AD, PD, and HD), there is considerable evidence suggesting that abnormalities in mitochondrial function contribute to the disease process. In each disorder, alterations in activities of enzymes involved in oxidative phosphorylation have been demonstrated including a decrease in activity of the α-ketoglutarate dehydrogenase complex in AD (97a) and a defect in complex I in PD (306b). Such abnormalities in mitochondrial energy metabolism may precede and contribute to the increased oxidative stress and perturbations in neuronal calcium homeostasis that occurs in each disorder. Interestingly, the metabolic deficits, and oxidative stress and calcium dysregulation, may not be limited to the brain cells affected in the disorders, as they have been documented in peripheral cells including fibroblasts and lymphocytes (95a, 306b). Based on these and additional data, Blass (23a) has introduced the concept of a "mitochondrial spiral," in which metabolic deficits result in oxyradical production and calcium dysregulation, to explain the pivotal role of mitochondrial alterations in neurodegenerative disorders. Both genetic and environmental factors may promote such neurodegenerative mitochondrial spirals (97a).

ALS involves degeneration of spinal cord motor neurons resulting in progressive paralysis and death (196, 301). Most cases of ALS are sporadic, but some result from mutations in the gene encoding the antioxidant enzyme Cu/Zn-SOD, which is located on chromosome 21 (62, 302). Transgenic mice expressing mutant Cu/Zn-SOD exhibit progressive motor neuron degeneration and a clinical phenotype remarkably similar to ALS patients (118, 368). Lipid peroxidation is increased in spinal cord motor neurons of ALS patients and transgenic mice (268, 269), and administration of vitamin E to Cu/Zn-SOD mutant mice delays disease onset (117), suggesting an important role for lipid peroxidation in the neurodegenerative process. In addition, creatine delayed the neurodegenerative process in a mouse model of ALS (168). ALS Cu/Zn-SOD mutations cause impairments in synaptic glucose and glutamate transport (114) and increase the vulnerability of motor neurons to excitotoxic injury by increasing oxidative stress and perturbing cellular calcium homeostasis (172, 185).

The remarkably large size of axons of motorneurons and their correspondingly high density of neurofilaments has led to the suggestion that impaired axonal transport plays a role in the pathogenesis of ALS. Studies of axonal transport in Cu/Zn-SOD mutant mice and of mice lacking or overexpressing neurofilament proteins support a role for impaired axonal transport in ALS (365, 383). Apoptosis of motor neurons in ALS is suggested by studies showing that levels of the proapoptotic protein Par-4 are increased in spinal cord motor neurons of ALS patients and Cu/Zn-SOD mutant mice (269), and levels of caspase activation are also increased in spinal cord tissue from Cu/Zn-SOD mutant mice (264). In addition, caspase inhibitors (190) and the antiapoptotic protein Bcl-2 (358) can protect motor neurons in Cu/Zn-SOD mutant mice. Moreover, neurotrophic factors that can prevent apoptosis of motor neurons in culture can also prevent motor neuron loss and disease progression in Cu/Zn-SOD mutant mice (243).

Genetic risk factors for stroke, an age-related neurological disorder, overlap with risk factors for coronary artery disease due to shared mechanisms of atherosclerosis and blood clot formation in each disorder. Familial hypercholesterolemia caused by mutations in the low-density lipoprotein receptor results in early-onset atherosclerotic vascular disease (334). Apolipoprotein E genotype affects risk of atherosclerosis (286). Polymorphisms in the apolipoprotein(s) gene and the gene for methylene tetrahydrofolate reductase have been shown to be prominent risk factors for atherosclerotic vascular disease (252). Polymorphisms in the fibrinogen and factor XIII genes have been linked to stroke (37), suggesting a contribution of genetic differences in regulation of clot formation to disease risk. An inherited stroke syndrome called CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) was recently linked to mutations in the Notch-3 gene on chromosome 19 (59), and the cellular and molecular alterations caused by these mutations are currently being investigated.

Collectively, the data that have accumulated in stud-

ies of the age-related neurodegenerative disorders described above suggest that each disorder shares abnormalities that contribute to neuronal dysfunction and death. The alterations include increased oxidative stress, dysregulation of protein trafficking and processing, metabolic impairment, and disruption of cellular calcium homeostasis. Genetic factors that cause, or increase risk of, a disorder do so by impacting directly or indirectly one or more of the cellular systems involved in oxyradical metabolism, protein processing, energy metabolism, and calcium homeostasis. Section IV describes a rapidly growing body of evidence demonstrating that age-related neurodegenerative cascades can be influenced by environmental factors.

IV. DIETARY FACTORS IN BRAIN AGING AND NEURODEGENERATIVE DISORDERS

There are numerous dietary factors that have been reported to affect brain physiology in ways that could, in theory, modify brain aging and the pathogenesis of neurodegenerative disorders (221a). These range from amino acids such as tryptophan (16) to caffeine and related stimulants (85) to omega-3 fatty acids (348). Many such dietary factors have been shown to affect mood or cognition. However, this review focuses on a more limited number of dietary factors for which considerable supportive experimental, clinical, and epidemiological data have accrued to justify the development of recommendations to the general public vis-à-vis risk reduction for neurodegenerative disorders. These factors include caloric intake, folic acid, and antioxidants.

A. Effects of Dietary Restriction on Brain Aging: Neuroplasticity and Neuroprotection

The mean and maximum life spans of many different organisms including yeast, roundworms, rodents, and monkeys can be increased by up to 50% simply by reducing their food intake (9, 176, 362). The incidence of age-related cancers, cardiovascular disease, and deficits in immune function is decreased in rodents maintained on such dietary restriction (DR) feeding regimens (362). Data from clinical and epidemiological studies in humans support the antiaging and disease prevention effects of DR. Thus a low-calorie diet decreases the risk of the most prominent age-related diseases in humans including cardiovascular disease, diabetes, and cancers (29, 179, 187). Recent findings reviewed in this section strongly suggest that DR can delay age-related functional deficits in the brain and may reduce the risk of major neurodegenerative disorders including AD, PD, and HD. DR may also increase resistance of neurons to acute insults such as stroke and severe epileptic seizures.

Biochemical and molecular analyses of the brains of old rats and mice that had been maintained on calorie-restricted diets reveal a retardation of changes that occur during aging of animals fed ad libitum including increases in levels of GFAP and oxidative damage to proteins and DNA (74, 245). Gene array analysis of the expression levels of thousands of genes in the brains of young rats and old rats that had been maintained on control or restricted diets revealed changes in gene expression in brain cells during aging and showed that DR can suppress many of those changes (180). Age-related changes in the expression of genes that encode proteins involved in innate immune responses, oxidative stress, and energy metabolism are counteracted by DR. This retardation of brain aging at the molecular level may underlie the preservation of brain function during aging in animals maintained on DR. For example, DR attenuates age-related deficits in learning and memory ability and motor function in rodents (140, 336). Studies of human populations suggest that DR can promote successful brain aging in humans. For example, epidemiological data suggest that the risk of developing AD, PD, and stroke is lower in individuals with a low calorie intake (30, 195, 235).

Beneficial effects of DR have been demonstrated in several of the animal models just described. The two DR protocols most commonly used in such studies are every-other-day feeding (the animals must go a whole day without food and then eat ad libitum on the next day) and paired feeding (the restricted animals are given food pellets that contain 30–40% fewer calories than the pellets given to the control animals). Both of these feeding regimens increase the life spans of rats and mice by 30–40% (103, 362). Rats maintained on DR for 2–4 mo exhibit increased resistance of hippocampal neurons to kainate-induced degeneration in a model relevant to the pathogenesis of AD and epilepsy; kainate selectively damages hippocampal pyramidal neurons and there is a profound deficit in learning and memory (31). When rats were maintained for several months on DR, damage to hippocampal neurons was decreased, and learning and memory were preserved compared with rats fed ad libitum (31). Studies of PS1 mutant knockin mice showed that the PS1 mutations increase the vulnerability of hippocampal and cortical neurons to excitotoxicity and apoptosis by a mechanism involving enhanced calcium release from the ER (108, 111). When PS1 mutant knockin mice were maintained on DR, they exhibited increased resistance of hippocampal CA1 and CA3 neurons to excitotoxic injury compared with mice fed ad libitum (388). Lipid peroxidation in the hippocampus after kainate administration was decreased in DR PS1 mutant mice, suggesting that suppression of oxidative stress is one mechanism whereby DR protects neurons (388).

DR has beneficial effects in animal models of PD and HD. The vulnerability of midbrain dopaminergic neurons

to MPTP toxicity was decreased in mice maintained on dietary restriction with more dopaminergic neurons surviving exposure to MPTP; the motor function of the mice was also improved in the restricted mice (69). Administration of the succinate dehydrogenase inhibitor (mitochondrial toxin) 3-nitropropionic acid (3-NP) to rats and mice results in selective degeneration of striatal neurons and motor impairment, a model of HD. When rats were maintained on DR for several months before administration of 3-NP, more striatal neurons survived exposure to 3-NP, and their motor function was improved (31). The ability of DR to improve outcome after a stroke was demonstrated in a rat model in which the middle cerebral artery was transiently occluded resulting in damage to the cerebral cortex and striatum supplied by that artery and unilateral motor dysfunction. When rats were maintained on DR for several months and then subjected to a stroke, they exhibited reduced brain damage and improved behavioral outcome (380). The neuroprotective effects of DR in animal models of several different neurodegenerative disorders suggest that low-calorie diets may prove beneficial in reducing the incidence and/or severity of the corresponding human neurodegenerative disorders.

Although the findings described in the preceding paragraphs document quite striking neuroprotective effects of DR, this dietary manipulation has not proven beneficial in all animal models of neurodegenerative disorders. For example, when one line of APP mutant transgenic mice was maintained on an every-other-day feeding regimen or was fed ad libitum, they died within 2–3 wk (267). Additional analyses in the latter study showed that the APP mutant mice were hypersensitive to the stress associated with fasting for an entire day and became severely hypoglycemic during the days they were without food. The APP mutant mice exhibited abnormalities in the regulation of the stress-responsive hypothalamic-pituitary-adrenal axis including altered glucocorticoid and blood glucose regulation in response to restraint stress. However, when every-other-day feeding was begun in APP mutant mice that were less than 3 mo of age, they survived, suggesting a role for age-dependent amyloid deposition in the aberrant stress response. Transgenic ALS mice expressing the G93A Cu/Zn-SOD mutation did not benefit from DR. When they were maintained on an every-other-day feeding regimen, the age of disease onset was unchanged (270). Moreover, once the ALS mice on DR became symptomatic, the disease progressed more rapidly and they died sooner than did ALS mice that were fed ad libitum. These findings are interesting in that they suggest that the pathogenic mechanism of action of the Cu/Zn-SOD mutation is not subject to modification by DR and/or that DR does not exert the same kind of neuroprotective action on spinal cord motor neurons that it exerts on neurons in the brain.

There is emerging evidence from studies of human populations that is consistent with the possibility that DR can reduce the risk of human neurodegenerative disorders. The following epidemiological data suggest that individuals with a low calorie intake may have reduced risk for AD and PD. There is a strong correlation between per capita food consumption and risk for AD (105). For example, the reported incidence of AD in China and Japan is approximately one-half that in the United States and Western Europe, and this is correlated with a lower calorie intake in China and Japan (1,600–2,000 calories/day) compared with the United States and Western Europe (2,500–3,000 calories/day). Overeating is also a major risk factor for stroke (30). Although there are caveats with the latter observations (for example, per capita food consumption is a very poor measure of energy intake, and disease diagnosis may differ among the countries), they are consistent with a protective effect of low-calorie diets against age-related neurodegenerative disorders. More convincing evidence that DR can protect against neurodegenerative disorders comes from population-based case-control studies by Mayeux and colleagues who found that individuals with the lowest daily calorie intakes had the lowest risk of AD (235) and PD (195). Interestingly, the risk of PD and AD was more strongly correlated with calorie intake than with weight or body mass index. More recently, Hendrie et al. (127) reported findings from a population-based longitudinal prospective study which indicate that the incidence of AD increases among individuals living in industrialized countries compared with genetically similar individuals that live in non-industrialized countries. Although the environmental factors that increase risk of AD in industrialized countries are not known, one clear difference between the two environments is calorie intake, which is much higher in industrialized countries. Together, the epidemiological and experimental data provide strong evidence that DR can reduce risk of AD, PD, and stroke, three of the most devastating neurodegenerative conditions in the elderly.

B. Cellular and Molecular Mechanisms Underlying the Neural Effects of Dietary Restriction

Because dietary restriction increases life span and reduces risk of many different age-related diseases including cardiovascular disease, diabetes, and cancers, it might be expected that it modifies shared biochemical cascades that lead to cell dysfunction and disease. In the case of neurodegenerative disorders, it is clear that while different genetic and environmental factors may initiate the neurodegenerative process in different disorders, a shared biochemical cascade ensues. Increased oxidative stress, perturbed cellular calcium homeostasis, and impaired energy metabolism occur in every neurodegenerative disorder studied to date (216, 219). These alterations

render neurons vulnerable to apoptosis, a biochemical cascade of molecular interactions involving proteins such as Par-4, Bcl-2 family members, and caspases (219).

It has been shown that DR can stabilize mitochondrial function and reduce oxidative stress in brain cells of rodents (113), and this may increase the resistance of neurons to many different types of genetic and environmental factors. DR can induce the expression of genes that encode proteins that promote neuronal survival and plasticity (Fig. 10). For example, levels of heat shock protein-70 (HSP-70) and glucose-regulated protein-78 (GRP-78) are increased in cortical, striatal, and hippocampal neurons of rats and mice maintained for several months on a dietary restriction feeding regimen (69, 380). HSP-70 and GRP-78 can protect neurons against excitotoxic and oxidative injury (197, 379), suggesting that their increased levels contribute to the neuroprotective effect of dietary restriction.

DR can induce the expression of several different neurotrophic factors in brain cells. Levels of BDNF are increased in neurons in the cerebral cortex, hippocampus, and striatum of rats and mice maintained on dietary restriction (67, 183). It is known that BDNF can protect neurons in culture and in vivo against excitotoxic, metabolic, and apoptotic insults (217). Levels of NGF (67) and CNTF (W. Duan and M. P. Mattson, unpublished data) are also increased by DR in one or more brain regions. Neurotrophic factors may protect neurons by stimulating the production of proteins that suppress oxidative stress (antioxidant enzymes and Bcl-2) and stabilize cellular calcium homeostasis (calcium-binding proteins and glutamate receptor subunits) (4, 98, 141, 233). BDNF and other neurotrophic factors might also counteract the adverse effects of aging on synaptic function because they can modify synaptic plasticity in ways that facilitate learning and memory (115, 146). Evidence for an important role for neurotrophic factors in the beneficial effects of DR in the brain is suggested by studies showing that infusion of a BDNF blocking antibody into the lateral ventricles of DR mice significantly attenuates the protective effect of DR (67).

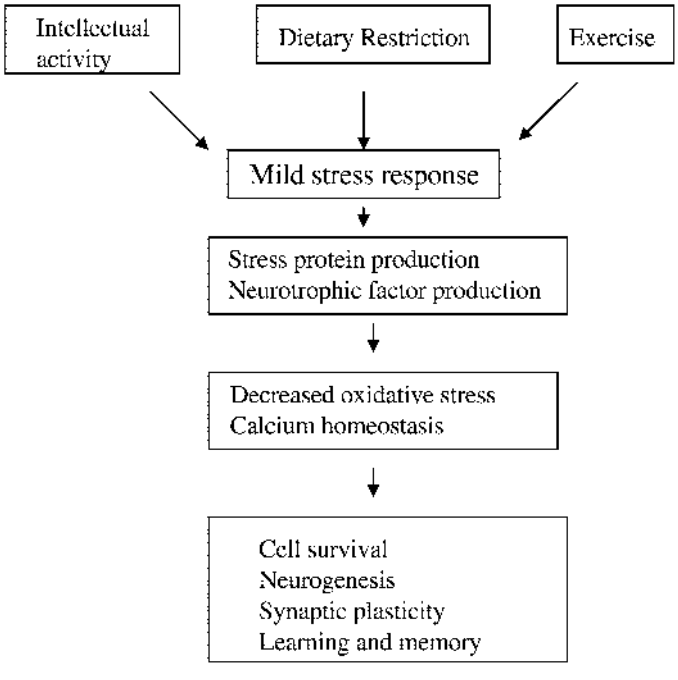

FIG. 10. Model of the mechanisms whereby dietary restriction, intellectual activity, and exercise promote neuronal survival and plasticity. Dietary restriction, activity in neuronal circuits, and physical exercise each induces a mild cellular stress response, as a result of energetic factors (reduced glucose availability in dietary restriction and increased energy demand during intellectual and physical activity, for example). Neurons respond to these stresses by activating signaling pathways that induce the expression of genes encoding proteins, such as growth factors and protein chaperones, that promote neuronal survival and plasticity (neurogenesis, neurite outgrowth, and synaptic plasticity).

Protein chaperones and neurotrophic factors are known to be induced by cellular stress, and it is therefore very likely that DR elicits a cellular stress response; this might result from decreased energy (glucose) availability to the cells, or from increased activity in neuronal circuits as the result of increased arousal due to hunger. Evidence supporting a role for a cellular stress response in the neuroprotective effects of DR was obtained in studies showing that the neuroprotective effects of DR can be mimicked by giving 2-deoxy-D-glucose (a nonmetabolizable analog of glucose) to rats and mice fed ad libitum. Animals given 2-deoxy-D-glucose exhibit increased levels of protein chaperones in their brain cells and increased resistance of neurons to excitotoxic, oxidative, and ischemic injury. Seizure-induced damage to hippocampal neurons is decreased, and learning and memory are preserved in rats given 2-deoxy-D-glucose (182). In the MPTP model of PD, mice given 2-deoxy-D-glucose exhibit decreased damage to dopaminergic neurons in the substantia nigra and a marked reduction in motor deficits (69). Rats admistered 2-deoxy-D-glucose also exhibit reduced damage to cortical and striatal neurons and improved behavioral outcome after transient occlusion of the middle cerebral artery (380).

The adult brain contains populations of cells that are capable of dividing and then differentiating into neurons (neurogenesis) or glial cells (gliogenesis). In rodents and humans, neural stem cells are most abundant in the subventricular zone and in the subgranular layer of the dentate gyrus of the hippocampus (91). It is thought that neural stem cells in the adult brain may provide a cellular reserve to replace neurons and glia that die as the result of various injuries and diseases. In support of the latter function of neural stem cells, it has been shown that neurogenesis can be stimulated by ischemic and excitotoxic brain injuries (194, 263). We discovered that caloric restriction can increase neurogenesis in the brains of rats and mice (183, 184). Animals that had been maintained on

a restricted diet or a control ad libitum diet for 3 mo were given five daily injections of the DNA precursor BrdU and were killed either 1 day or 3–4 wk after the last BrdU injection. Numbers of BrdU-positve (newly generated) cells in the dentate gyrus were quantified by unbiased stereological methods. At the 1-day time point there was no difference in BrdU-labeled cells between calorie-restricted and control animals, indicating that calorie restriction does not affect the proliferation rate of the neural stem cells. Instead, DR resulted in a significant increase in the number of BrdU-positive cells remaining at the 3- or 4-wk time points, suggesting that DR promotes the survival of newly generated neural cells (183, 184). Many of the newly generated cells become dentate granule neurons. Although not yet established, it is conceivable that BDNF plays a role in the enhanced survival of newly generated neural stem cells in the dentate gyrus of rats maintained on DR because BDNF is known to have a similar effect on neural stem cells. When taken together with the fact that learning and memory is preserved in aging rodents maintained on dietary restriction (140), and that suppression of NPC proliferation can impair learning and memory (322), it is possible that DR promotes maintenance of cognitive function during aging by enhancing neurogenesis.

Interestingly, increasing data suggest that the brain may control life span by regulating energy metabolism of the entire organism (222). Because systems that regulate energy metabolism, such as the insulin signaling pathway, are believed to play major roles in the aging process (366), they are likely to have an important influence on brain aging. Key signaling pathways involved in the regulation of energy metabolism by the brain include BDNF, insulin-like growth factors, and neuropeptides that control feeding behavior in the brain, and insulin in peripheral tissues (Fig. 11).

Although DR clearly has beneficial effects in the nervous system, there are several aspects of its mechanism of action that remain to be explained. For example, animals maintained on DR exhibit increased levels of glucocorticoids consistent with an increased level of stress (250a). In animals fed ad libitum, increased glucocorticoids associated with chronic stress have been shown to promote neuronal degeneration (306a) and impair neurogenesis (35a). Why then does DR prevent neuronal degeneration and enhance neurogenesis? One possibility is that the specific responses of neural cells to DR stress are different from responses to the kinds of chronic psychosocial stress that have been shown to be deleterious to the brain. Indeed, we have documented a different profile of changes in the expression of glucocorticoid and mineralocorticoid receptors in the hippocampus in response to DR than are seen in animals subjected to psychosocial stress (183a). The ability of DR to increase neurotrophic factor production and the expression of cytoprotective stress proteins may override any potentially deleterious effects of elevated glucocorticoids. Indeed, stress and glucocorticoids decrease the expression of BDNF in the hippocampus (327a), and BDNF can protect neurons against the adverse effects of glucocorticoids (254a). Therefore, DR elicits cellular and molecular responses that allow enhanced activation of the hypothalamic-pituitary-adrenal axis to occur, but without the deleterious effects that might otherwise result from this heightened state of neuroendocrine function.

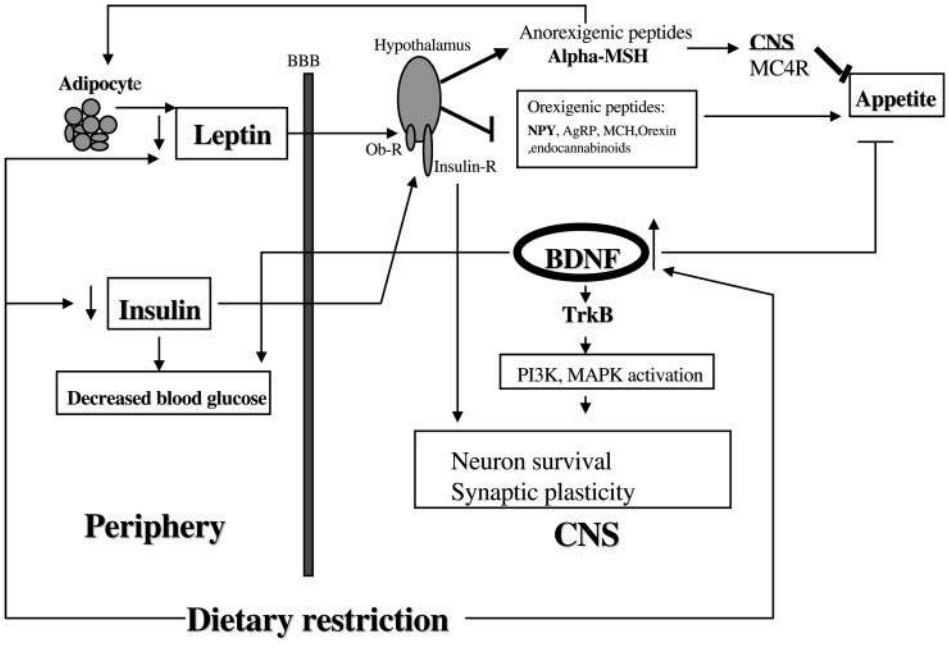

FIG. 11. Regulation of energy metabolism by interactions between the brain and peripheral tissues. The brain controls feeding behaviors through complex neural circuits involving sensory inputs, cortical and hippocampal connections, and hypothalamic interactions with higher brain regions via neurotransmitters and modulators such as serotonin and neuropeptide Y as well as circulating hormones such as leptins. See text for further information. AgRP, agouti-related protein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; MAPK, mitogen-activated protein kinase; MC4R, receptor for MSH; MCH, melanocyte concentrating hormone; MSH, melanocyte stimulating hormone; NPY, neuropeptide Y; Ob-R, leptin receptor; PI3K, phosphatidylinositol 3-kinase.

C. Folic Acid

Humans cannot synthesize folic acid and therefore must obtain it in the diet; major sources of folate are green vegetables, citrus fruits, liver, and whole grains. The predominant dietary folates are 5-methyltetrahydrofolate and formyltetrahydrofolate, which are readily transported across the intestinal epithelium. The reason that many processed foods contain folic acid is that it was recognized decades ago that babies born to women that have a diet deficient in folic acid are at increased risk of birth defects. The fact that such birth defects most commonly involve the nervous system (spina bifida, meningocoele, encephalocoele, and anencephaly) indicates that neural cells may be particularly sensitive to folic acid. Folic acid deficiency causes abnormalities in cell proliferation, differentiation, and survival. The important role for folic acid in development of the nervous system is further demonstrated by genetic alterations in methyltetrahydrofolate reductase (MTHFR), which decreases enzyme activity, resulting in decreased folic acid levels and increased risk of neural tube defects (319, 328). In addition, targeted gene deletion of the folic acid transporter results in embryonic lethality in mice (277). Recent studies have demonstrated direct consequences of folic acid deficiency on neurons by showing that simply depriving cultured embryonic brain cells of folate can induce apoptosis (programmed cell death) in developing neurons (171).

Folic acid acts as a cofactor in many different biochemical reactions by donating and accepting one-carbon units (314). Methionine synthase, a vitamin B_{12}-dependent enzyme, plays an important role in facilitating the conversion of extracellular 5-methyltetrahydrofolate to monoglutamyl tetrahydrofolate, a form of folic acid that can be readily used in nucleotide biosynthesis. Membrane transporters for folic acid are expressed in cells throughout the body including brain cells, and it is therefore likely that folic acid plays a critical role in one-carbon metabolism in neural cells (325). An array of biochemical reactions require methyl groups, and the normal dietary supply of methyl groups is insufficient to meet these demands and must be synthesized from the one-carbon folic acid pool. Folic acid (5′-methyltetrahydrofolate) is required for conversion of methionine to *S*-adenosylmethionine (SAM), the latter being the major methyl donor in most biochemical reactions (Fig. 12). Folic acid deficiency results in depletion of SAM and a reduction in the methylation of cytosine in DNA. The decreased DNA methylation that can result from folic acid deficiency may enhance gene transcription and DNA strand breakage which can trigger malignant transformation (279, 359).

During the past decade it has become clear that folic acid deficiency can increase risk for coronary artery disease and stroke (28, 77) and that this adverse effect of folic acid deficiency is associated with an elevation in plasma homocysteine levels (104). Homocysteine is produced from methionine by demethylation (Fig. 12), and homocysteine levels are kept low by its remethylation to methionine by a reaction requiring folic acid and vitamin B_{12}, or by conversion of homocysteine to cystathionine by the activity of the enzyme cystathionine-β-synthase (CBS). Alterations in the expression or enzyme activities

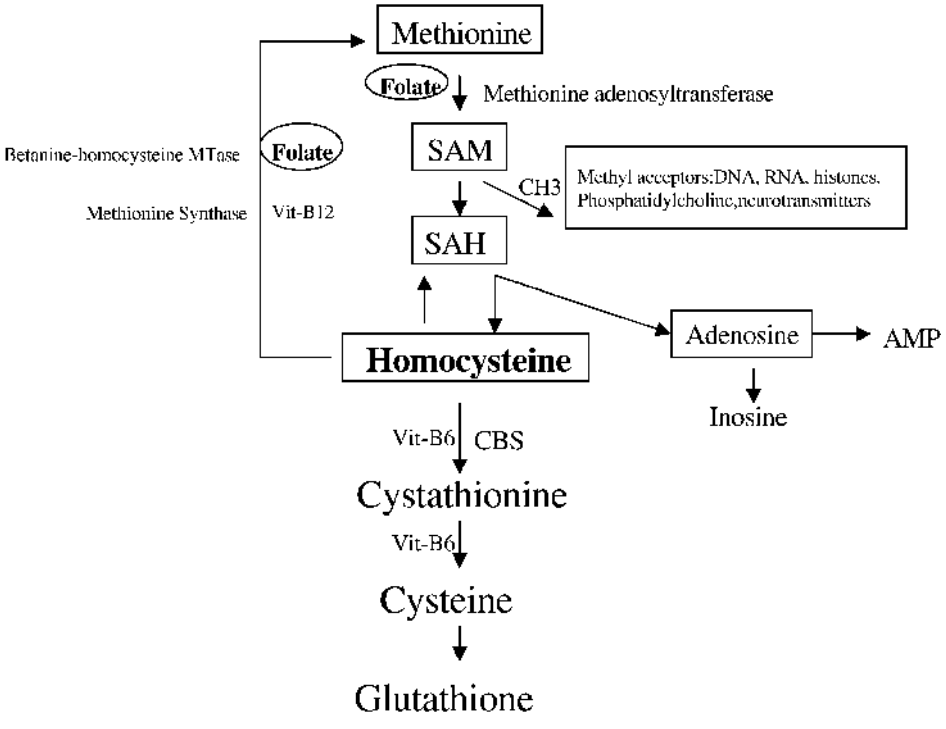

FIG. 12. The involvement of folic acid and homocysteine in one-carbon metabolism. Homocysteine is a metabolite of methionine, an amino acid that plays a key role in the generation of methyl groups required for numerous biochemical reactions; homocysteine can either be remethylated to methionine by enzymes that require folic acid or catabolized by cystathionine-β-synthase (CBS), a vitamin B_6-dependent enzyme, to form cysteine. SAH, *S*-adenosyl-L-homocysteine; SAM, *S*-adenosyl-L-methionine; MTase, methyltransferase.

of methionine synthase and CBS can affect levels of homocysteine. Indeed, levels of homocysteine are increased in the cerebrospinal fluid of children with mutations in CBS (340) and may contribute to the abnormalities in brain function documented in such patients. Homocysteine can damage cells by inducing oxidative stress and DNA damage and impairing DNA repair (170, 171).

The importance of folic acid in the developing nervous system suggests the possibility that folic acid deficiency and elevated homocysteine levels might also have adverse effects in the adult nervous system. Possible links between folic acid, homocysteine, and neurological disorders have therefore been looked for and found. Data have accumulated that suggest links between dietary folic acid, homocysteine levels, and the pathogenesis of AD and PD. AD patients have significantly lower levels of folic acid and higher levels of homocysteine in their blood compared with neurologically normal age-matched control patients (49, 188). Elevated levels of homocysteine have also been reported in PD patients (175). A caveat with the studies just described is that all analyses were performed on blood samples from symptomatic patients, and it is therefore unclear whether decreased folic acid levels and elevated homocysteine levels precede and contribute to the neurodegenerative process. Thus the nutritional abnormalities might result from altered diet in these sick patients. Additional evidence from studies of patients and animal models described below do, however, support roles for homocysteine in the early pathogenesis of neurodegenerative disorders.

The major risk factor for AD, PD, and stroke is age, and studies have shown that homocysteine levels progressively increase with age (27). Deficiencies in folic acid and vitamin B_{12} may also contribute to the declines in cognitive and other neurological functions that occur during normal aging (315) including psychiatric disorders (25). A study of geriatric patients admitted to a psychiatric hospital revealed that individuals with below median values of folic acid and vitamin B_{12} performed worse on tests of cognitive function than did individuals with above-median levels of folic acid and vitamin B_{12} (17). On the other hand, elevated plasma homocysteine levels were not associated with cognitive impairment in centenarians (292). Genetic variations in the MTHFR gene may be associated with risk of PD with individuals with the C677T genotype (which increases homocysteine levels) being at increased risk (374). Mice deficient in MTHFR exhibit hyperhomocysteinemia and neuropathological alterations (45), consistent with a loss of function of the enzyme in humans with disease-promoting forms of the enzyme.

Animal and cell culture models of neurodegenerative disorders have provided evidence that folic acid deficiency and elevated homocysteine levels can render neurons vulnerable to dysfunction and death. When APP mutant mice, which develop progressive amyloid deposition in their brains, were maintained on a low-folate/high-homocysteine diet, neurons in the hippocampus degenerated (171). This contrasted with nontransgenic mice in which the experimental diet did not cause degeneration of neurons. Folic acid deficiency may render neurons vulnerable to being damaged and killed by amyloid because exposure of cultured rat hippocampal neurons to folic acid-deficient medium or to homocysteine increases the vulnerability of the neurons to being killed by Aβ (170, 171). It has also been reported that dietary folic acid deficiency sensitizes mice to MPTP-induced PD-like pathology and motor dysfunction (68). Direct application of homocysteine into either the substantia nigra or striatum exacerbated dopamine depletion, neuronal degeneration, and motor dysfunction. Moreover, homocysteine increased the vulnerability of cultured human dopamine-producing cells to rotenone and iron. The ability of folic acid deficiency and elevated homocysteine levels to sensitize neurons to amyloid and MPTP toxicities suggests a mechanism whereby dietary folic acid may modify risk of AD and PD.

The mechanism whereby homocysteine damages and kills neurons has been elucidated in recent studies. Homocysteine induced DNA damage in cultured hippocampal neurons, which resulted from a combination of impaired DNA repair and increased oxidative stress, as indicated by increased uracil misincorporation and increased oxidative modification of DNA bases (171). Homocysteine-induced DNA damage can trigger a programmed cell death pathway involving poly(ADP-ribose) polymerase and the tumor suppressor protein p53, leading to mitochondrial dysfunction and activation of death proteases (170). Impaired DNA repair may play a role in the pathogenesis of AD because fibroblasts from AD patients exhibit a defect in repair of DNA lesions (189, 297). In cultured dopaminergic cells, homocysteine can exacerbate oxidative stress, mitochondrial dysfunction, and apoptosis in cells exposed to the pesticide rotenone or the pro-oxidant Fe^{2+}. The dopaminergic cells can be protected against the adverse effects of homocysteine by administration of the antioxidant uric acid and by an inhibitor of poly(ADP-ribose) polymerase (68).

Alterations in folate and one-carbon metabolism may also contribute to several other neurodegenerative conditions. For example, the huntingtin protein interacts with CBS (26), and alterations in folate metabolism have been documented in patients with ALS (376). ALS is a disorder in which spinal cord motor neurons degenerate resulting in progressive paralysis and death. It has been proposed that an abnormality in folate metabolism accounts for the reported reduction of RNA and the elevation of taurine in the nervous system of ALS patients (376). Homocysteine can also induce seizures in rodents (173), and alterations in homocysteine levels may occur in human

epilepsy patients (313), suggesting a possible contribution to epilepsy.

D. Antioxidants

There are tens of thousands of natural and synthetic compounds that possess antioxidant activity, and a rapidly growing number of these agents have been reported to have beneficial effects in one or more experimental models of age-related disorders. It is beyond the scope of this article to review the field of antioxidants and brain aging; instead, examples of results obtained with several of the most widely studied antioxidants are presented. These include vitamin E, coenzyme Q_{10}, lipoic acid, creatine, and Ginko biloba extract.

Vitamin E (α/γ-tocopherol) is a lipid-soluble antioxidant that is very effective in suppressing membrane lipid peroxidation. Data have accumulated that suggest that dietary supplementation with vitamin E can reduce risk of cardiovascular disease and many cancers (64). Chronic treatment of rodents with vitamin E can preserve learning and memory function, which otherwise declines during aging (330). Treatment of rat hippocampal slices with α-tocopherol enhanced long-term potentiation of synaptic transmission, a cellular correlate of learning and memory (370). Clinical trials of vitamin E in AD patients have yielded positive results with patients receiving this antioxidant exhibiting a slowing of disease progression compared with those receiving placebo (106). Vitamin E may counteract the effects of aging and neurodegenerative disorders by suppressing membrane lipid peroxidation and thereby preserving membrane transporter function and stabilizing cellular ion homeostasis. As evidence, vitamin E can protect cultured neurons and synaptosomes against dysfunction and death induced by Aβ (102, 204) and can protect against amyloid-induced learning and memory deficits in adult rats (371). Vitamin E has also been reported to be effective in animal and cell culture models of ALS (117, 172, 265) and PD (299), although clinical benefit in human patients has not yet been established.

Coenzyme Q_{10} (ubiquinone) is associated with the mitochondrial oxidative phosphorylation enzyme complexes where it serves an antioxidant function. Administration of ubiquinone to rodents can enhance learning and memory (156). Ubiquinone protected cultured neural cells against insults relevant to the pathogenesis of AD (273). Dietary supplementation with ubiquinone resulted in increased resistance of midbrain dopaminergic neurons to MPTP-induced damage in a mouse model of PD (13) and increased resistance of striatal neurons to the succinate dehydrogenase inhibitor malonate in a rodent model of HD (12). Clinical trials of ubiquinone have proven effective in treating patients with myocardial infarction (324) and cancers (129), although it is not established that ubiquinone supplementation can reduce risk of these disorders. The potential of dietary supplementation with ubiquinone to prevent or treat age-related neurodegenerative disorders remains to be determined.

α-Lipoic acid is an endogenous disulfide compound that is present in small amounts in most animal cells where it functions as a coenzyme in the α-ketoglutarate dehydrogenase and pyruvate dehydrogenase enzyme complexes (208). The antioxidant and cytoprotective actions of lipoic acid have been documented in a variety of cell culture and animal models of age-related disease (237). A number of clinical trials of lipoic acid have been completed or are in progress in patients with cardiovascular disease, cancer, and diabetes. Dietary supplementation with lipoic acid has proven beneficial in normalizing glucose metabolism in patients with type II diabetes (143). Lipoic acid and the related compound dihydrolipoate were effective in protecting cultured neurons against death induced by hypoxia, glutamate, and iron and were effective in reducing focal ischemic brain injury in vivo (248, 283). Lipoic acid was also effective in protecting cultured rat cortical neurons against death induced by Aβ (384). Dietary supplementation with lipoic acid increased the survival of Cu/Zn-SOD mutant transgenic mice (8), suggesting that this antioxidant may prove beneficial in ALS patients.

Creatine increases phosphocreatine levels in muscle and brain cells and may thereby improve cellular energetics and reduce oxyradical production (220). Creatine is now widely employed as a dietary supplement by athletes to improve their performance (79). Creatine significantly reduced brain damage in a rat model of traumatic brain injury, suggesting that it may not only enhance the performance of athletes, but may also improve the outcome of head injuries (338). Head injury is an important cause of morbidity and mortality in the elderly (296). The possibility that creatine may protect against neurodegenerative conditions has been tested in several animal models. Dietary supplementation with creatine delayed motor dysfunction and increased survival in a transgenic mouse model of HD (7), protected dopaminergic neurons against MPTP toxicity in mice (212), and increased the survival of Purkinje cells in a transgenic mouse model of spinocerebellar ataxia type 1 (155). Preliminary results of a recent clinical trial of creatine supplementation in ALS patients suggest that it can increase muscle strength (236).

The public has recently been barraged with advertisements touting the health benefits of Gingko biloba with a particular emphasis on its benefits for the brain (251). Ginkgo biloba extract enhanced performance of aged mice in a learning and memory task (50). In a rat model of severe diabetes, Gingko biloba was effective in improving learning and memory performance (132). Ginkgo biloba supplementation in a double-blind, place-

bo-controlled, 14-wk, parallel group, repeated assessment, multi-center trial proved effective in improving cognitive function in healthy middle-aged subjects (363). However, other trials of Ginkgo extracts on memory performance in normal adults (247) and elderly patients with mild cognitive impairment (350) have not revealed a significant effect of this dietary supplement (247). Ginkgo extracts can protect cultured cortical neurons against damage induced by iron (107) and protect cultured PC12 cells against Aβ toxicity (11, 373). Ginkgo extract reduced damage to dopaminergic neurons caused by MPTP in a mouse model of PD (287). Blindness due to degeneration of photoreceptors occurs in many aged individuals, and it was shown that Ginkgo biloba extract can protect photoreceptors against light-induced damage (289). Overall, the available data suggest that Ginkgo biloba has beneficial effects in the nervous system, although further studies will be required before this dietary supplement can be recommended for primary prevention of neurodegenerative disorders.

Other antioxidants that have been associated with reduced risk or disease and/or have exhibited neuroprotective effects in cell culture and animal models relevant to age-related neurodegenerative disorders include estrogen, carotenoids, uric acid, glutathione, and *N*-acetylcysteine. Epidemiological data and clinical studies suggest that estrogens can improve memory and reduce risk of dementia during aging (318). Estrogen can protect cultured neurons against death induced by Aβ (101, 278) and can protect cortical neurons against ischemic injury in vivo (73). However, clinical trials of estrogen in AD patients have not resulted in clear beneficial effects and epidemiological studies aimed at determining whether estrogens can prevent AD have generated mixed results. Individuals over the age of 65 that have higher levels of β-carotene perform better in learning and memory tests compared with individuals with low β-carotene levels (275). Lycopene is a carotenoid that has been suggested to protect against heart disease, stroke, and certain cancers (290, 295). Lycopene can protect cultured hippocampal neurons against Aβ and glutamate toxicity (Fig. 13). Levels of uric acid have been reported to be decreased in patients with AD (200, 345). Uric acid administration to adult rats reduced focal ischemic brain injury and improved functional outcome in a stroke model (378). Uric acid is remarkably effective in protecting cultured neurons against insults relevant to AD and PD, including exposure to Aβ and iron (111, 160, 161, 378). Glutathione is a major antioxidant in the brain and can protect neurons against a variety of oxidative insults in experimental models relevant to the pathogenesis of AD, PD, ALS, and stroke (161, 205, 265). *N*-acetylcysteine has proven effective in reducing age-related deficits in learning and memory (209). Encouraging beneficial effects of *N*-acetylcysteine supplementation were recently reported in a clinical trial in patients with probable AD (2), suggesting that this antioxidant may soon be used as a dietary supplement for patients in the early stages of neurodegenerative disorders.

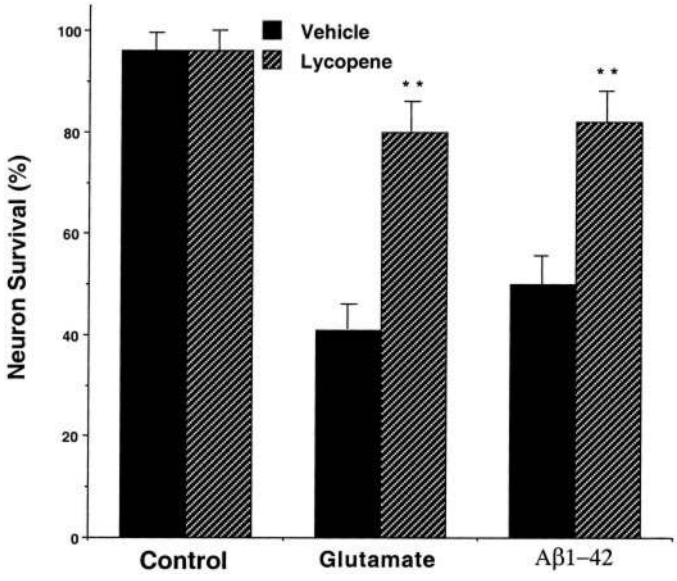

FIG. 13. The antioxidant lycopene protects hippocampal neurons against excitotoxicity and against apoptosis induced by amyloid β-peptide. Primary rat hippocampal cell cultures were pretreated for 16 h with 1 μM lycopene and were then exposed to saline (control), 10 μM glutamate, or 1 μM Aβ-(1—42) for 24 h. Neuron survival was quantified, and values are means ± SD of determinations made in 4 cultures per condition. $^{**}P < 0.01$ compared with corresponding value for vehicle-treated cultures (ANOVA with Scheffé post hoc tests).

V. BEHAVIORAL MODIFICATION OF BRAIN AGING

Studies performed during the past decade strongly suggest that our daily behaviors can affect the molecular composition and cellular structure of our brain. When adult rodents are housed in complex environments or exercised on a regular basis, there are increases in the complexity of dendrites in cortical neurons and increased numbers of synapses (153). These structural changes are associated with increased production of certain neurotrophic factors and with enhanced performance on learning and memory and motor function tasks. Other behavioral factors may have a negative impact on the brain, with the best-documented example being psychosocial stress (239). The molecular and cellular mechanisms responsible for beneficial or detrimental effects of different behaviors on the brain are beginning to be understood and may involve changes in neurotrophic factor, neurotransmitter, and hormonal signaling pathways. With respect to aging and age-related neurodegenerative disorders, the available data suggest that those behaviors that enhance

dendritic complexity and synaptic plasticity also promote successful aging and decrease risk of neurodegenerative disorders. Collectively, the emerging data suggest that behavioral factors can have a major impact on the outcome of brain aging.

A. Intellectual Activity

Epidemiological studies have documented an inverse relationship between educational attainment and risk for AD such that more educated persons are at reduced risk (81). Particularly interesting are data suggesting that intellectual function in early life can affect risk of AD. Thus, in a study of a population of nuns in Minnesota, Snowdon et al. (329) showed that nuns with the best linguistic abilities as young adults were at reduced risk for AD. One interpretation of these data is that intellectual activity is neuroprotective. Animal studies are consistent with this interpretation. Greenough and co-workers (22, 167) showed that rats raised in complex environments exhibit increased complexity of dendritic arbors and synapses in the hippocampus and cerebellum, suggesting an increased functional reserve. During aging, synaptic density decreases in the hippocampus in rats, and maintenance of the rats in a complex environment can prevent such age-related synaptic loss (306). In addition, when rodents are raised in complex environments in which they have many objects to play with, neurogenesis is enhanced and learning and memory ability is improved (164, 254, 377). Complex environments, which can be equated with intellectual activity in humans, may also increase resistance of neurons to injury and promote recovery after injury. As evidence, functional deficits caused by bilateral lesions of the frontal cortex are ameliorated when rats are maintained in complex environments, and this was correlated with reduced damage to cortical neurons (169). Further studies have shown that, in addition to enhancing synaptic connectivity and increasing resistance of neurons to injury, complex environments can improve outcome after ischemic stroke in rats (151). Similarly, maintenance of rats in complex environments improves learning and memory performance in a water maze test after lesion of cholinergic basal forebrain neurons (352). The latter findings suggest that intellectual activity can enhance recovery of function after brain injury.

The cellular and molecular mechanisms whereby complex environments enhance neuronal plasticity and resistance to injury are beginning to be revealed. Presumably, the increased activity in neural circuits that results from intellectual activity leads to long-term changes in gene expression that play a role in its beneficial effects. Indeed, rats raised in a complex environment exhibit changes in the upregulation of DL-α-amino-3-hydroxy-5-methylisoxazole-propionic acid (AMPA; a glutamate receptor agonist) binding in response to calcium in hippocampal neurons, without a change in levels of AMPA receptor subunit mRNA or protein levels (92). Levels of several different neurotrophic factors are increased in the brains of animals maintained in complex environments compared with control animals maintained in simple environments. Levels of BDNF and NGF are increased in cerebral cortex, hippocampus, basal forebrain, and hindbrain, and levels of both the high- and low-affinity NGF receptors are increased in the basal forebrain of rats maintained in a complex environment (138). There are striking similarities in the effects of DR and intellectual activity on neurotrophic factor expression and neuronal plasticity, suggesting a shared mechanism underlying their beneficial effects in the brain (Fig. 10).

B. Exercise

Exercise benefits not only the musculoskeletal and cardiovascular systems, but it also benefits the brain. Regular vigorous exercise improves mood and cognition; these effects of exercise have been clearly established in controlled studies (84). Studies of elderly populations suggest that regular exercise can also promote maintenance of cognitive function during aging (78, 349). Other studies have shown that regular exercise in elderly men is particularly effective in improving cognitive performance on tasks that require visuospatial processing (317). Fourteen-month-old rats that exercised regularly (swimming 1 h/day, 5 days/wk for 9 wk) exhibited improved performance in a learning and memory task and reduced levels of membrane lipid peroxidation and oxidative damage to DNA (285). For example, mice allowed access to a running wheel exhibit increased neurogenesis and improved learning and memory compared with "couch potato" mice (351). Exercise results in an increase in the level of BDNF in the hippocampus in rats (304), suggesting a role for BDNF in the beneficial effects of exercise on brain function and plasticity. Another neurotrophic factor upregulated in the brain in response to learning and exercise is bFGF (100). The latter study showed that the increase in bFGF levels was associated with an increase in astrocyte density, suggesting a potential role for astrocytes in the beneficial effects of exercise in the brain. Further data supporting a beneficial effect of exercise on the brain come from epidemiological studies in humans which show that regular vigorous physical activity can reduce risk for ischemic stroke (181); although it has not been established that prior physical activity can improve outcome after a stroke, this would seem plausible. Physical activity can also benefit the brain after injury. For example, exercise after brain injury improved functional outcome in rats, and the improved outcome was associated with enhanced structural plasticity in the motor cortex (152).

VI. SYNAPSES AND AGING: EMERGING CONCEPTS

The numbers and size of synapses change during aging and response to environmental stimuli. During successful brain aging, numbers of synapses may or may not decrease depending on the brain region; in brain regions in which synapse numbers do decrease, the size of the remaining synapses may increase, perhaps as a compensatory mechanism. For example, in a study of superior-middle frontal cortex (area 9) in cognitively normal individuals ranging in age from 20 to 89 yr, there was no change in synapse density in lamina III and V (308). On the other hand, a decrease in synaptic density occurs in the lateral septal nucleus in a subset of aged rats (309). In striking contrast to normal aging, clear and profound decreases in synapse numbers occur in brain regions involved in learning and memory in AD (307). Interestingly, synapse loss also occurs in the cerebral cortex of many patients with HD and PD (382). Studies of animal models of age-related neurodegenerative disorders (AD, HD, and PD) have documented synapse loss and have provided evidence that the synapse degeneration occurs early in the disease process, well before cell death (256, 259, 298).

Abnormalities in synaptic signal transduction pathways and associated functional deficits may occur during aging and may be early and pivotal events in the pathogenesis of neurodegenerative disorders. Several findings point to synaptic alterations occurring very early in AD and being central to the cognitive deficits and neuronal death. Studies of APP (41) and PS1 (263) mutant transgenic mice have documented alterations in synaptic plasticity that occur without evidence of synapse loss or cell death. Aβ is deposited at high levels in synaptic regions, presumably because its protein precursor (APP) is axonally transported. Exposure of isolated synaptic terminals to Aβ results in impairment of ion-motive ATPases and glucose and glutamate transporters (162). Aβ and oxidative stress can also induce apoptotic biochemical cascades in synapses and dendrites, including increased production of Par-4, mitochondrial alterations, and caspase activation (70, 234). Neurotrophic factors (115) and estrogen (159) that may protect against AD can preserve synaptic transporter functions during exposure to Aβ. PS1 mutations result in perturbed synaptic calcium homeostasis and thereby promote synapse dysfunction and degeneration (15). Although fewer studies have addressed the issue of synaptic dysfunction in PD and HD, studies of animal models are consistent with perturbations in synaptic function and initiation of apoptotic biochemical cascades occurring early in the disease process (66, 71).

The vast majority of signal transduction pathways that regulate structural and functional plasticity, and survival of neurons are localized in synapses. Some of these synaptic signaling systems may be particularly sensitive to age-related increases in levels of oxidative stress and decreases in energy availability (Fig. 14). For example, oxidative stress leading to membrane lipid peroxidation can impair the coupling of muscarinic cholinergic receptors to the GTP-binding protein G_{q11}, apparently as the result of covalent modification of G_{q11} by the lipid peroxidation product 4-hydroxynonenal (23, 163). Age-related decreases in levels of neurotrophic factors and/or their receptors have been reported (125, 381), and on the basis of the localization of neurotrophic factor receptors in synapses, compromised neurotrophic signaling would be expected to promote synapse degeneration and cell death. On the other hand, cellular adaptations to aging may include an enhancement of neurotrophic signaling that supports synaptic plasticity (Figs. 1 and 14).

Age- and disease-related synaptic dysfunction and degeneration may be subject to modification by dietary and behavioral factors. Studies of cortical synaptosomes prepared from rats maintained on calorie-restricted or control diets have shown that caloric restriction can increase the resistance of synapses to oxidative and metabolic insults, as indicated by relative preservation of glucose and glutamate transport and mitochondrial function (113). 2-Deoxy-D-glucose administration exerted similar beneficial effects on synapses (116). The amounts of HSP-70 and GRP-78 were increased in synaptosomes from calorie-restricted rats and rats given 2-deoxy-D-glucose, demonstrating that energy restriction bolsters the ability of synapses to cope with the oxidative and metabolic stress associated with aging. As described in section V, increased activity in neuronal circuits due to intellectual or physical activities may prevent age-related dysfunction and loss of synapses. Presumably, many of the same adaptive changes that occur in neurons subjected to dietary restriction, including increased neurotrophic factor signaling and protein chaperone production, also occur in response to intellectual and physical activity. These changes benefit synapses directly by enhancing their ability to tolerate oxidative and metabolic stress.

VII. IMPLICATIONS FOR PREVENTION AND TREATMENT OF NEURODEGENERATIVE DISORDERS

Because of advances in the prevention and treatment of cardiovascular disease and cancers, many more people are living beyond the age of 70, and neurological disorders of aging have therefore become more common causes of disability and death. As described above, research efforts on neurodegenerative disorders have rapidly expanded in the past decade and have greatly advanced our understanding of the molecular and cellular mechanisms that

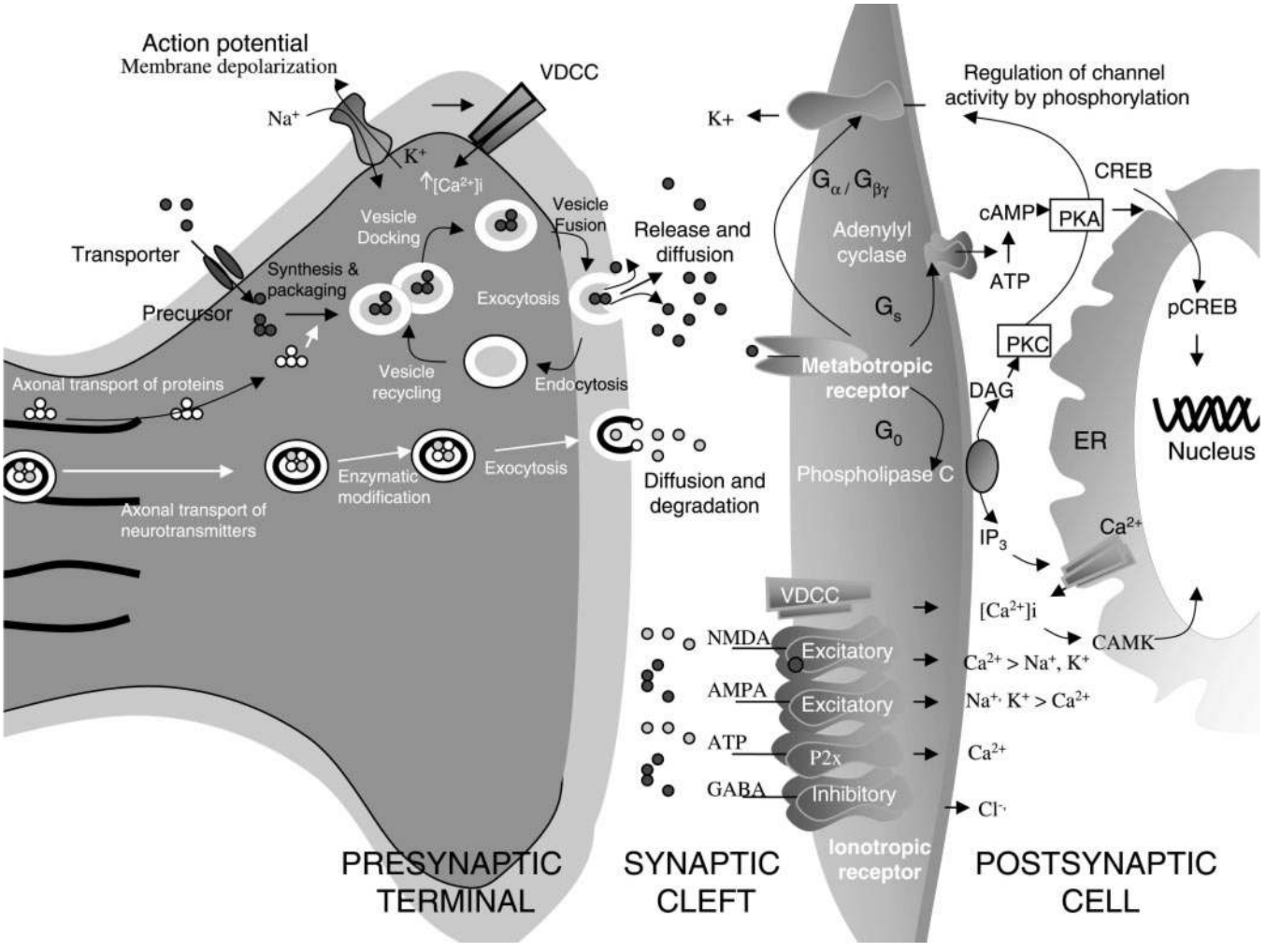

FIG. 14. Synaptic signaling systems that are subject to modification by aging, genes, and diet. Glutamate, the major excitatory neurotransmitter in the brain, activates several different types of ionotropic rectors (including AMPA and NMDA receptors) resulting in membrane depolarization and calcium influx. Glutamate can also activate metabotropic receptors coupled to inositol phospholipid hydrolysis and the production of inositol 1,4,5-trisphosphate (IP_3), which triggers calcium release from endoplasmic reticulum stores, and diacylglycerol which activates protein kinase C. GABA is the major inhibitory neurotransmitter in the brain and, by hyperpolarizing the membrane, can counteract the excitatory effects of glutamate. Calcium influx induced by glutamate can activate transcription factors resulting in changes in gene expression that mediate effects of glutamate on synaptic plasticity and cell survival. AMPA, L-α-amino-3-hydroxy-5-methylisoxazole-4-propionate; CAMK, calcium/calmodulin-dependent protein kinase; CREB, cAMP response element binding protein; DAG, diacylglycerol; NMDA, *N*-methy-D-aspartate; PKA, cAMP-dependent protein kinase; PKC, protein kinase C; VDCC, voltage-dependent calcium channel.

result in neuronal dysfunction and death, and the genetic and environmental risk factors for the disorders. Basic and clinical research in this field have reached a point where recommendations can be made to the general population concerning how they can reduce their risk of age-related neurodegenerative disorders. Moreover, effective treatments for symptomatic patients are beginning to emerge.

As with other major age-related diseases, including cardiovascular disease, type 2 diabetes, and some cancers, the most effective means of reducing risk for neurodegenerative disorder may be to modify one's diet and behaviors. As described in section IV*A*, caloric restriction during adult life may be particularly effective in reducing risk of age-related neurodegenerative disorders. A link between high cholesterol levels and risk of stroke has been established, and recent findings suggest that high cholesterol levels may also increase risk of AD (54), suggesting that a reduced fat diet may help ensure a healthy brain as one ages. Links between pesticides and PD (20) and dietary toxins and ALS (335) have been reported. The latter findings suggest that reducing exposure to such environmental toxins may reduce the incidence of these disorders. New dietary and behavioral approaches for promoting healthy brain aging will undoubtedly emerge from ongoing research. By analogy with physical exercise

benefiting the musculoskeletal and cardiovascular systems, mental exercise may improve the ability of brain cells to cope with the aging process.

Can pharmacological interventions retard brain aging? Antioxidants such as vitamin E, coenzyme Q_{10}, lipoic acid, and ginko extract, and supplements such as creatine that enhance cellular energy maintenance, may provide some degree of protection (7, 11–13, 50, 107, 119, 155, 168, 212, 354, 384). Recent studies have evaluated dietary supplements that mimic the physiological effects of caloric restriction for their ability to enhance resistance of neurons to age-related disease (69, 116, 380). Suppressing apoptosis using agents that target key proteins in the cell death process, such as p53 and caspases, is another potentially effective strategy (55, 72). It has also been suggested that cholesterol-lowering statins may protect the brain against age-related neurodegenerative disease via actions on the vasculature or directly on neurons (83, 149). In addition to preventative strategies that affect pathways of neuronal degeneration or neuroprotection that are shared among age-related neurodegenerative disorders, novel disease-specific approaches are also being developed. In the case of AD, for example, drugs that inhibit β- and γ-secretases and thereby reduce Aβ production are being developed (48), as are amyloid vaccine-based approaches (139).

Finding cures for age-related brain dysfunction and disease is a worthy, but elusive and often frustrating, goal. By the time that patients with AD, PD, HD, and stroke become symptomatic, extensive damage to neuronal circuits has already occurred. Treatment strategies must therefore focus on halting further neuronal degeneration and promoting reestablishment of neuronal circuits. Recent advances, many of which are described in this review, suggest that the goal of curing patients with age-related neurodegenerative disorders is worth pursuing. One reason for optimism is that the extent of neuronal death in PD and AD patients during the early period of the diseases may not be as great as initially thought, because many dysfunctional neurons may be able to recover (95). In addition, neural stem cells may be capable of replacing lost neurons (91). Moreover, it may be possible to manipulate cell adhesion and signaling pathways in ways that enhance neurite outgrowth and synaptogenesis (312). Neurotrophic factors and agents that stimulate their production as well as drugs that enhance synaptic transmission are currently in clinical trials, as are several antioxidants. In addition, trials are in progress to determine the safety and efficacy of transplantation of neural stem cells in PD patients. "Cocktail" treatments (e.g., multiple antioxidants) have proven most efficacious in preclinical studies and are therefore likely to also achieve the greatest effects in human patients. In this regard, it is of considerable interest that dietary supplementation with fruits and vegetables rich in multiple antioxidants is proving effective in counteracting age-related brain dysfunction in studies in rodents (154).

Preclinical studies in animal models of neurodegenerative disorders have identified several approaches that are efficacious in preventing neuronal degeneration and/or restoring lost function. Administration of Aβ to APP mutant transgenic mice results in reduced amyloid deposition and increased clearance of amyloid deposits in the brain and improved learning and memory performance (244, 310). The latter studies have led to a clinical trial of an amyloid "vaccine" in AD patients. Unfortunately, the clinical trial was recently halted because several patients developed encephalitis. Another promising approach for removing amyloid deposits from the brains of AD patients is based on a role for metals, copper, iron, and zinc in particular, to promote aggregation of Aβ. An older study suggested a benefit of the iron chelator desferroxamine in AD patients (53), and recent preclinical studies in APP mutant mice (47) have led to a clinical trial of a copper chelator in AD patients. Epidemiological and animal studies suggest that antioxidants (282), estrogenic steroids (239), and anti-inflammatory drugs (136) can reduce risk of AD, presumably by reducing damage to neurons and microglial activation. Amyloid deposition and oxidative stress in AD may facilitate excitotoxic neuronal death (224). Glutamate receptor antagonists are therefore being evaluated for the treatment of AD patients (144).

Several types of drugs are in development for the treatment of PD patients. Because excitotoxicity is thought to be involved in the degeneration of dopaminergic neurons, *N*-methyl-D-aspartate receptor antagonists are being tested in animal models of, and patients with, PD and related movement disorders (61). Similar antiexcitotoxic approaches are being applied to HD and stroke (33). Synthetic inhibitors of the proapoptotic protein p53 protected dopaminergic neurons against death and improved motor function, in a mouse model of PD (Duan). As described above, dietary supplementation with creatine has proven beneficial in mouse models of ALS and PD (168, 212).

The kinds of data obtained in the studies of rodent models of brain aging and neurodegenerative disorders described above suggest that DR can increase health span of the brain and effectively protect neurons against the dysfunction and death that occurs in neurodegenerative disorders. However, it remains to be conclusively demonstrated that the results of the animal studies are directly applicable to humans. Clinical trials of DR in humans will be difficult to perform because they will require long time periods (many years to decades) of compliance and extensive resources. Nevertheless, data emerging from a study of life-long DR in rhesus monkeys begun here at the National Institute on Aging 14 years ago strongly suggest that DR increases life span in primates (176a). In our view, there is no doubt that DR is beneficial for the nervous system of humans, just as it benefits every other organ system studied. The major hurdle

to be crossed, as was the case with the problem of smoking as a risk factor for cardiovascular and pulmonary diseases, is educating the public as to the benefits of DR and identifying behavioral and even pharmacological approaches for preventing and treating food addiction (as with nicotine addiction).

How might genetic factors that cause or increase risk of age-related neurodegenerative disorders be dealt with directly? Autosomal dominant mutations, such as those in the genes encoding APP, presenilins, α-synuclein, huntingtin, and Cu/Zn-SOD, could be eliminated in a single generation. This would be accomplished by identifying those that harbor the mutations at an early age and ensuring, by counseling abstinence or other means, that they do not pass on the defective gene. Genetic screening to identify those at increased risk of a disorder (e.g., individuals with an E4 allele of apolipoprotein E) would allow aggressive preventative dietary and pharmacological interventions. In the more distant future it may be possible to eliminate "bad" genes using gene therapy approaches, although many technical hurdles need to be crossed. Until such breakthroughs occur, we must continue to pursue dietary, behavioral, and drug-based approaches for increasing the health span of the brain.

Address for reprint requests and other correspondence: M. P. Mattson, Laboratory of Neurosciences, National Institute on Aging GRC 4F01, 5600 Nathan Shock Dr., Baltimore, MD 21224 (E-mail: mattsonm@grc.nia.nih.gov).

REFERENCES

1. Abeliovich A, Schmitz Y, Farinas I, Choi-Lundberg D, Ho WH, Castillo PE, Shinsky N, Verdugo JM, and Armanini M. Mice lacking alpha-synuclein display functional deficits in the nigrostriatal dopamine system. *Neuron* 25: 239–252, 2000.
2. Adair JC, Knoefel JE, and Morgan N. Controlled trial of *N*-acetylcysteine for patients with probable Alzheimer's disease. *Neurology* 57: 1515–1517, 2001.
3. Albin R, Young AB, and Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci* 12: 366–375, 1989.
4. Allsopp TE, Kiseley S, Wyatt S, and Davies AM. Role of Bcl-2 in the brain-derived neurotrophic factor survival response. *Eur J Neurosci* 7: 1266–1272, 1995.
5. Altar CA. Neurotrophins and depression. *Trends Pharmacol Sci* 20: 59–61, 1999.
6. Ancolio K, Marambaud P, Dauch P, and Checler F. Alpha-secretase-derived product of beta-amyloid precursor protein is decreased by presenilin 1 mutations linked to familial Alzheimer's disease. *J Neurochem* 69: 2494–2499, 1997.
7. Andreassen OA, Dedeoglu A, Ferrante RJ, Jenkins BG, Ferrante KL, Thomas M, Friedlich A, Browne SE, Schilling G, Borchelt DR, Hersch SM, Ross CA, and Beal MF. Creatine increases survival and delays motor symptoms in a transgenic animal model of Huntington's disease. *Neurobiol Dis* 8: 479–491, 2001.
8. Andreassen OA, Dedeoglu A, Friedlich A, Ferrante KL, Hughes D, Szabo C, and Beal MF. Effects of an inhibitor of poly(ADP-ribose) polymerase, desmethylselegiline, trientine, and lipoic acid in transgenic ALS mice. *Exp Neurol* 168: 419–424, 2001.
9. Ashrafi K, Lin SS, Manchester JK, and Gordon JI. Sip2p and its partner snf1p kinase affect aging in *S. cerevisiae*. *Genes Dev* 14: 1872–1885, 2000.
10. Bartke A, Coschigano K, Kopchick J, Chandrashekar V, Mattison J, Kinney B, and Hauck S. Genes that prolong life: relationships of growth hormone and growth to aging and life span. *J Gerontol A Biol Sci Med Sci* 56: B340–B349, 2001.
11. Bastianetto S, Ramassamy C, Dore S, Christen Y, Poirier J, and Quirion R. The Ginkgo biloba extract (EGb 761) protects hippocampal neurons against cell death induced by beta-amyloid. *Eur J Neurosci* 12: 1882–1890, 2000.
12. Beal MF, Henshaw DR, Jenkins BG, Rosen BR, and Schulz JB. Coenzyme Q_{10} and nicotinamide block striatal lesions produced by the mitochondrial toxin malonate. *Ann Neurol* 36: 882–888, 1994.
13. Beal MF, Matthews RT, Tieleman A, and Shults CW. Coenzyme Q_{10} attenuates the 1 methyl-4-phenyl-1,2,3,tetrahydropyridine (MPTP) induced loss of striatal dopamine and dopaminergic axons in aged mice. *Brain Res* 783: 109–114, 1998.
14. Beere HM, Wolf BB, Cain K, Mosser DD, Mahboubi A, Kuwana T, Tailor P, Morimoto RI, Cohen GM, and Green DR. Heat-shock protein 70 inhibits apoptosis by preventing recruitment of procaspase-9 to the Apaf-1 apoptosome. *Nat Cell Biol* 2: 469–475, 2000.
15. Begley JG, Duan W, Chan S, Duff K, and Mattson MP. Altered calcium homeostasis and mitochondrial dysfunction in cortical synaptic compartments of presenilin-1 mutant mice. *J Neurochem* 72: 1030–1039, 1999.
16. Bell C, Abrams J, and Nutt D. Tryptophan depletion and its implications for psychiatry. *Br J Psychiatry* 178: 399–405, 2001.
17. Bell IR, Edman JS, Marby DW, Satlin A, Dreier T, Liptzin B, and Cole JO. Vitamin B_{12} and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin nondeficient population. *Biol Psychiatry* 27: 125–137, 1990.
18. Ben-Ari Y, Khazipov R, Leinekugel X, Caillard O, and Gaiarsa JL. $GABA_A$, NNDA and AMPA receptors: a developmentally regulated "menage a trois." *Trends Neurosci* 20: 523–529, 1997.
19. Bertoni-Freddari C, Fattoretti P, Paoloni R, Caselli U, Galeazzi L, and Meier-Ruge W. Synaptic structural dynamics and aging. *Gerontology* 42: 170–180, 1996.
20. Betarbet R, Sherer TB, Mackenzie G, Garcia-Osuna M, Panov AV, and Greenamyre JT. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci* 3: 1301–1306, 2000.
21. Bjorklund A. Cell replacement strategies for neurodegenerative disorders. *Novartis Found Symp* 231: 7–15, 2000.
22. Black JE, Sirevaag AM, Wallace CS, Savin MH, and Greenough WT. Effects of complex experience on somatic growth and organ development in rats. *Dev Psychobiol* 22: 727–752, 1989.
23. Blanc EM, Kelly JF, Mark RJ, and Mattson MP. 4-Hydroxynonenal, an aldehydic product of lipid peroxidation, impairs signal transduction associated with muscarinic acetylcholine and metabotropic glutamate receptors: possible action on $G\alpha_{q/11}$. *J Neurochem* 69: 570–580, 1997.

23A. Blass JP. The mitochondrial spiral. An adequate cause of dementia in the Alzheimer's syndrome. *Ann NY Acad Sci* 924: 170–183, 2000.

24. Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, Harley CB, Shay JW, Lichsteiner S, and Wright WE. Extension of life-span by introduction of telomerase into normal human cells. *Science* 279: 349–352, 1998.
25. Bottiglieri T. Folate, vitamin B_{12}, and neuropsychiatric disorders. *Nutr Rev* 54: 382–390, 1996.
26. Boutell JM, Wood JD, Harper PS, and Jones AL. Huntingtin interacts with cystathionine beta-synthase. *Hum Mol Genet* 7: 371–378, 1998.
27. Brattstrom L, Lindgren A, Israelsson B, Andersson A, and Hultberg B. Homocysteine and cysteine: determinants of plasma levels in middle-aged and elderly subjects. *J Intern Med* 236: 633–641, 1994.
28. Brattstrom L, Lindgren A, Israelsson B, Malinow MR, Norrving B, Upson B, and Hamfelt A. Hyperhomocysteinaemia in stroke: prevalence, cause, and relationships to type of stroke and stroke risk factors. *Eur J Clin Invest* 22: 214–221, 1992.
29. Brochu M, Poehlman ET, and Ades PA. Obesity, body fat distribution, and coronary artery disease. *J Cardiopulm Rehabil* 20: 96–108, 2000.
30. Bronner LL, Kanter DS, and Manson JE. Primary prevention of stroke. *N Engl J Med* 333: 1392–1400, 1995.

31. Bruce-Keller AJ, Umberger G, McFall R, and Mattson MP. Food restriction reduces brain damage and improves behavioral outcome following excitotoxic and metabolic insults. *Ann Neurol* 45: 8–15, 1999.
32. Bui NT, Livolsi A, Peyron JF, and Prehn JH. Activation of nuclear factor κB and Bcl-x survival gene expression by nerve growth factor requires tyrosine phosphorylation of IκBα. *J Cell Biol* 152: 753–764, 2001.
33. Bullock R. Strategies for neuroprotection with glutamate antagonists. Extrapolating from evidence taken from the first stroke and head injury studies. *Ann NY Acad Sci* 765: 272–278, 1995.
34. Butterfield DA, Howard BJ, Yatin S, Allen KL, and Carney JM. Free radical oxidation of brain proteins in accelerated senescence and its modulation by *N-tert*-butyl-α-phenylnitrone. *Proc Natl Acad Sci USA* 94: 674–678, 1997.
35. Cakatay U, Telci A, Kayali R, Tekeli F, Akcay T, and Sivas A. Relation of oxidative protein damage and nitrotyrosine levels in the aging rat brain. *Exp Gerontol* 36: 221–229, 2001.
35A. Cameron HA, Tanapa TP, and Gould E. Adrenal steroids and *N*-methyl-D-aspartate receptor activation regulate neurogenesis in the dentate gyrus of adult rats through a common pathway. *Neuroscience* 82: 349–354, 1998.
36. Caruso C, Candore G, Romano GC, Lio D, Bonafe M, Valensin S, and Franceschi C. Immunogenetics of longevity. Is major histocompatibility complex polymorphism relevant to the control of human longevity? A review of literature data. *Mech Ageing Dev* 122: 445–462, 2001.
37. Catto AJ. Genetic aspects of the hemostatic system in cerebrovascular disease. *Neurology* 57: S24–S30, 2001.
38. Chan SL, Griffin WS, and Mattson MP. Evidence for caspase-mediated cleavage of AMPA receptor subunits in neuronal apoptosis and Alzheimer's disease. *J Neurosci Res* 57: 315–323, 1999.
39. Chan SL, Mayne M, Holden CP, Geiger JD, and Mattson MP. Presenilin-1 mutations increase levels of ryanodine receptors and calcium release in PC12 cells and cortical neurons. *J Biol Chem* 275: 18195–18200, 2000.
40. Chan SL, Pedersen WA, Zhu H, and Mattson MP. Numb modifies neuronal vulnerabililty to amyloid β-peptide in an isoform-specific manner by a mechanism involving altered calcium homeostasis: implications for neuronal death in Alzheimer's disease. *Neuromol Med.* In press.
41. Chapman PF, White GL, Jones MW, Cooper-Blacketer D, Marshall VJ, Irizarry M, Younkin L, Good MA, Bliss TV, Hyman BT, Younkin SG, and Hsiao KK. Impaired synaptic plasticity and learning in aged amyloid precursor protein transgenic mice. *Nat Neurosci* 2: 271–276, 1999.
42. Chartier-Harlin MC, Crawford F, Houlden H, Warren A, Hughes D, Fidani L, Goate A, Rossor M, Roques P, and Hardy J. Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene. *Nature* 353: 844–846, 1991.
43. Checkoway H, Farin FM, Costa-Mallen P, Kirchner SC, and Costa LG. Genetic polymorphisms in Parkinson's disease. *Neurotoxicology* 19: 635–643, 1998.
44. Chen M. Alzheimer's alpha-secretase may be a calcium-dependent protease. *FEBS Lett* 417: 163–167, 1997.
45. Chen Z, Karaplis AC, Ackerman SL, Progribny IP, Melnyk S, Lussier-Cacan S, Chen MF, Pai A, John SW, Smith RS, Bottiglieri T, Bagley P, Selhub J, Rudnicki MA, James SJ, and Rozen R. Mice deficient in methylenetetrahydrofolate reductase exhibit hyperhomocysteinemia and decreased methylation capacity, with neuropathology and aortic lipid deposition. *Hum Mol Genet* 10: 433–443, 2001.
46. Cheng B and Mattson MP. IGF-I and IGF-II protect cultured hippocampal and septal neurons against calcium-mediated hypoglycemic damage. *J Neurosci* 12: 1558–1566, 1992.
47. Cherny RA, Atwood CS, Xilinas ME, Gray DN, Jones WD, Mclean CA, Barnham KI, Volitakis I, Fraser FW, Kim Y, Huang X, Goldstein LE, Moir RD, Lim JT, Beyreuther K, Zheng H, Tanzi RE, Masters CL, and Bush AI. Treatment with a copper-zinc chelator markedly and rapidly inhibits beta-amyloid accumulation in Alzheimer's disease transgenic mice. *Neuron* 30: 665–676, 2001.
48. Citron M. Secretases as targets for the treatment of Alzheimer's disease. *Mol Med Today* 6: 392–397, 2000.
49. Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, and Ueland PM. Folate, vitamin B_{12}, and serum total homocysteine levels in confirmed Alzheimer disease. *Arch Neurol* 55: 1449–1455, 1998.
50. Cohen-Salmon C, Venault P, Martin B, Raffalli-Sebille MJ, Barkats M, Clostre F, Pardon MC, Christen Y, and Chapouthier G. Effects of Ginkgo biloba extract (EGb 761) on learning and possible actions on aging. *J Physiol Paris* 91: 291–300, 1997.
51. Cooper B. Nature, nurture and mental disorder: old concepts in the new millennium. *Br J Psychiatry Suppl* 40: S91–S101, 2001.
52. Cournil A and Kirkwood TB. If you would live long, choose your parents well. *Trends Genet* 17: 233–235, 2001.
53. Crapper McLachlan DR, Dalton AJ, Kruck TP, Bell MY, Smith WL, Kalow W, and Andrews DF. Intramuscular desferrioxamine in patients with Alzheimer's disease. *Lancet* 337: 1304–1308, 1991.
54. Cucchiara B and Kasner SE. Use of statins in CNS disorders. *J Neurol Sci* 187: 81–89, 2001.
55. Culmsee C, Zhu Z, Yu QS, Chan SL, Camandola S, Guo Z, Greig N, and Mattson MP. A synthetic inhibitor of p53 protects neurons against death induced by ischemic and excitotoxic insults, and amyloid beta-peptide. *J Neurochem* 77: 220–228, 2001.
56. Dacosta CA, Ancolio K, and Checler F. Wild-type but not Parkinson's disease-related ala-53 → Thr mutant α-synuclein protects neuronal cells from apoptotic stimuli. *J Biol Chem* 275: 24065–24069, 2000.
57. Daniels J, McGuffin P, Owen MJ, and Plomin R. Molecular genetic studies of cognitive ability. *Hum Biol* 70: 281–296, 1998.
58. Darnell RB. Immunologic complexity in neurons. *Neuron* 21: 947–950, 1998.
59. Davous P. Cadasil: a review with proposed diagnostic criteria. *Eur J Neurol* 5: 219–233, 1998.
60. De Benedictis G, Carrieri G, Varcasia O, Bonafe M, and Franceschi C. Inherited variability of the mitochondrial genome and successful aging in humans. *Ann NY Acad Sci* 908: 208–218, 2000.
61. Del Dotto P, Pavese N, Gambaccini G, Barnardini S, Metman LV, Chase TN, and Bonuccelli U. Intravenous amantadine improves levadopa-induced dyskinesias: an acute double-blind placebo-controlled study. *Mov Disord* 16: 515–520, 2001.
62. Deng HX, Hentati A, Tainer JA, Iqbal Z, Cayabyah A, Hung WY, and Gezoff ED. Amyotrophic lateral sclerosis and structural defects in Cu,Zn superoxide dismutase. *Science* 261: 1047–1051, 1993.
63. De Strooper B, Annaert W, Cupers P, Saftig P, Craessaerts K, Mumm JS, Schroeter EH, Schrijvers V, Wolfe MS, Ray WJ, Goate A, and Kopan R. A presenilin-1-dependent gamma-secretase-like protease mediates release of Notch intracellular domain. *Nature* 398: 518–522, 1999.
64. Diplock AT. Will the "good fairies" please prove to us that vitamin E lessens human degenerative disease? *Free Radic Res* 26: 565–583, 1997.
65. Dirnagl U, Iadecola C, and Moskowitz MA. Pathobiology of ischaemic stroke: an integrated view. *Trends Neurosci* 22: 391–397, 1999.
66. Duan W, Guo Z, and Mattson MP. Participation of par-4 in the degeneration of striatal neurons induced by metabolic compromise with 3-nitropropionic acid. *Exp Neurol* 165: 1–11, 2000.
67. Duan W, Guo Z, and Mattson MP. Brain-derived neurotrophic factor mediates an excitoprotective effect of dietary restriction in mice. *J Neurochem* 76: 619–626, 2001.
68. Duan W, Ladenheim B, Cutler RG, Cadet JL, and Mattson MP. Dietary folate deficiency and elevated homocysteine levels endanger dopaminergic neurons in models of Parkinson's disease. *J Neurochem* 80: 101–110, 2002.
69. Duan W and Mattson MP. 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.
70. Duan W, Rangnekar VM, and Mattson MP. Prostate apoptosis response-4 production in synaptic compartments following apoptotic and excitotoxic insults: evidence for a pivotal role in mitochondrial dysfunction and neuronal degeneration. *J Neurochem* 72: 2312–2322, 1999.
71. Duan W, Zhang Z, Gash DM, and Mattson MP. Participation of prostate apoptosis response-4 in degeneration of dopaminergic

neurons in models of Parkinson's disease. *Ann Neurol* 46: 587–597, 1999.
72. DUAN W, ZHU Z, LADENHEIM B, YU Q, GUO Z, CUTLER RG, CADET JL, GREIG NH, AND MATTSON MP. Synthetic p53 inhibitors preserve dopaminergic neurons and motor function in experimental Parkinsonism. *Ann Neurol.* In press.
73. DUBAL DB, KASHON ML, PETTIGREW LC, REN JM, FINKLESTEIN SP, RAU SW, AND WISE PM. Estradiol protects against ischemic injury. *J Cereb Blood Flow Metab* 18: 1253–1258, 1998.
74. DUBEY A, FORSTER MJ, LAL H, AND SOHAL RS. Effect of age and caloric intake on protein oxidation in different brain regions and on behavioral functions of the mouse. *Arch Biochem Biophys* 333: 189–197, 1996.
75. DUFF K, ECKMAN C, ZEHR C, YU X, PRADA CM, PEREZ-TUR J, HUTTON M, BUEE L, HARIGAYA Y, YAGER D, MORGAN D, GORDON MN, HOLCOMB L, REFOLO L, ZENK B, HARDY J, AND YOUNKIN S. Increased amyloid-beta42(43) in brains of mice expressing mutant presenilin 1. *Nature* 383: 710–713, 1996.
76. DUYAO M, AMBROSE C, MYERS R, NOVELLETTO A, PERSICHETTI F, FRONTALI M, FOLSTEIN S, AND ROSS C. Trinucleotide repeat length instability and age of onset in Huntington's disease. *Nat Gen* 4: 387–392, 1993.
77. ELKIND MS AND SACCO RL. Stroke risk factors and stroke prevention. *Semin Neurol* 18: 429–440, 1998.
78. ELWARD K AND LARSON EB. Benefits of exercise for older adults. A review of existing evidence and current recommendations for the general population. *Clin Geriatr Med* 8: 35–50, 1992.
79. ENGELHARDT M, NEUMANN G, BERBALK A, AND REUTER I. Creatine supplementation in endurance sports. *Med Sci Sports Exercise* 30: 1123–1129, 1998.
80. ESTUS S, TUCKER HM, VAN ROOYEN C, WRIGHT S, BRIGHAM EF, WOGULIS M, AND RYDEL RE. Aggregated amyloid-beta protein induces cortical neuronal apoptosis and concomitant "apoptotic" pattern of gene induction. *J Neurosci* 17: 7736–7745, 1997.
81. EVANS DA, HEBERT LE, BECKETT LA, SCHERR PA, ALBERT MS, CHOWN MJ, PILGRAM DM, AND TAYLOR JO. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Arch Neurol* 54: 1399–1405, 1997.
82. FAIN JN, DEL MAR NA, MEADE CA, REINER A, AND GOLDOWITZ D. Abnormalities in the functioning of adipocytes from R6/2 mice that are transgenic for the Huntington's disease mutation. *Hum Mol Genet* 10: 145–152, 2001.
83. FASSBENDER K, SIMONS M, BERGMANN C, STROICK M, LUTJOHANN D, KELLER P, RUNZ H, KUHL S, BERTACH T, VON BERGMANN K, HENNERICI M, BEYREUTHER K, AND HARTMANN T. Simvastatin strongly reduces levels of Alzheimer's disease β-amyloid peptides Aβ 42 and Aβ 40 in vitro and in vivo. *Proc Natl Acad Sci USA* 98: 5856–5861, 2001.
84. FOX KR. The influence of physical activity on mental well-being. *Public Health Nutr* 2: 411–418, 1999.
85. FREDHOLM BB, BATTIG K, HOLMEN J, NEHLIG A, AND ZVARTAU EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 51: 83–133, 1999.
86. FRYDMAN J. Folding of newly translated proteins in vivo: the role of molecular chaperones. *Annu Rev Biochem* 70: 603–647, 2001.
87. FU W, KILLEN M, CULMSEE C, DHAR S, PANDITA TK, AND MATTSON MP. The catalytic subunit of telomerase is expressed in developing brain neurons and serves a cell survival-promoting function. *J Mol Neurosci* 14: 3–15, 2000.
89. FU W, LUO H, PARTHASARATHY S, AND MATTSON MP. Catecholamines potentiate amyloid beta-peptide neurotoxicity: involvement of oxidative stress, mitochondrial dysfunction, and perturbed calcium homeostasis. *Neurobiol Dis* 5: 229–243, 1998.
90. FURUKAWA K, BARGER SW, BLALOCK EM, AND MATTSON MP. Activation of K^+ channels and suppression of neuronal activity by secreted beta-amyloid-precursor protein. *Nature* 379: 74–78, 1996.
91. GAGE FH. Mammalian neural stem cells. *Science* 287: 1433–1438, 2000.
92. GAGNE J, GELINAS S, MARTINOLI MG, FOSTER TC, OHAYON M, THOMPSON RF, BAUDRY M, AND MASSICOTTE G. AMPA receptor properties in adult rat hippocampus following environmental enrichment. *Brain Res* 799: 16–25, 1998.
93. GAMES D, ADAMS D, ALESSANDRINI R, BARBOUR R, BERTHELETTE P, BLACKWELL C, CARR T, CLEMENS J, DONALDSON T, AND GILLESPIE F. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature* 373: 523–527, 1995.
94. GARY DS AND MATTSON MP. Integrin signaling via the PI3-kinase-Akt pathway increases neuronal resistance to glutamate-induced apoptosis. *J Neurochem* 76: 1485–1496, 2001.
95. GASH DM, ZHANG Z, AND GERHARDT G. Neuroprotective and neurorestorative properties of GDNF. *Ann Neurol* 44: S121–S125, 1998.
95a. GASPARINI L, RACCHI M, BINETTI G, TRABUCCHI M, SOLERTES B, ALKON D, ETCHEBERRIGARAY R, GIBSON G, BLASS J, PAOLETTI R, AND GOVONI S. Peripheral markers in testing pathophysiological hypotheses and diagnosing Alzheimer's disease. *FASEB J* 12: 17–34, 1998.
96. GETHING MJ. Role and regulation of the ER chaperone BiP. *Semin Cell Dev Biol* 10: 465–472, 1999.
97. GEULA C, WU CK SAROFF D, LORENZO A, YUAN M, AND YANKNER BA. Aging renders the brain vulnerable to amyloid beta-protein neurotoxicity. *Nat Med* 4: 827–831, 1998.
97a. GIBSON GE, PARK LC, SHEU KF, BLASS JP, AND CALINGASAN NY. The alpha-ketoglutarate dehydrogenase complex in neurodegeneration. *Neurochem Int* 36: 97–112, 2000.
98. GLAZNER GW AND MATTSON MP. Differential effects of BDNF, ADNF9, and TNFalpha on levels of NMDA receptor subunits, calcium homeostasis, and neuronal vulnerability to excitotoxicity. *Exp Neurol* 161: 442–452, 2000.
99. GOKHAN S AND MEHLER MF. Basic and clinical neuroscience applications of embryonic stem cells. *Anat Rec* 265: 142–156, 2001.
100. GOMEZ-PINILLA F, SO V, AND KESSLAK JP. Spatial learning and physical activity contribute to the induction of fibroblast growth factor: neural substrates for increased cognition associated with exercise. *Neuroscience* 85: 53–61, 1998.
101. GOODMAN Y, BRUCE AJ, CHENG B, AND MATTSON MP. Estrogens attenuate and corticosterone exacerbates excitotoxicity, oxidative injury, and amyloid beta-peptide toxicity in hippocampal neurons. *J Neurochem* 66: 1836–1844, 1996.
102. GOODMAN Y AND MATTSON MP. Secreted forms of beta-amyloid precursor protein protect hippocampal neurons against amyloid beta-peptide-induced oxidative injury. *Exp Neurol* 128: 1–12, 1994.
103. GOODRICK CL, INGRAM DK, REYNOLDS MA, AND FREEMAN CIDER NL JR. Differential effects of intermittent feeding and voluntary exercise on body weight and lifespan in adult rats. *J Gerontol* 38: 36–45, 1983.
104. GRAHAM IM AND O'CALLAGHAN P. The role of folic acid in the prevention of cardiovascular disease. *Curr Opin Lipidol* 11: 577–587, 2000.
105. GRANT W. Dietary links to Alzheimer's disease. *Alz Dis Rev* 2: 42–55, 1997.
106. GRUNDMAN M. Vitamin E and Alzheimer disease: the basis for additional clinical trials. *Am J Clin Nutr* 71: 630S–636S, 2000.
107. GUIDETTI C, PARACCHINI S, LUCCHINI S, CAMBIERI S, CAMBIERI M, AND MARZATICO F. Prevention of neuronal cell damage induced by oxidative stress in-vitro: effect of different Ginkgo biloba extracts. *J Pharm Pharmacol* 53: 387–392, 2001.
108. GUO Q, FU W, SOPHER BL, MILLER MW, WARE CB, MARTIN GM, AND MATTSON MP. Increased vulnerability of hippocampal neurons to excitotoxic necrosis in presenilin-1 mutant knock-in mice. *Nat Med* 5: 101–106, 1999.
109. GUO Q, FU W, XIE J, LUO H, SELLS SF, GEDDES JW, BONDADA V, RANGNEKAR V, AND MATTSON MP. Par-4 is a mediator of neuronal degeneration associated with the pathogenesis of Alzheimer's disease. *Nature Med* 4: 957–962, 1998.
110. GUO Q, FURUKAWA K, SOPHER BL, PHAM DG, XIE J, ROBINSON N, MARTIN GM, AND MATTSON MP. Alzheimer's PS-1 mutation perturbs calcium homeostasis and sensitizes PC12 cells to death induced by amyloid beta-peptide. *Neuroreport* 8: 379–383, 1996.
111. GUO Q, SEBASTIAN L, SOPHER BL, MILLER MW, WARE CB, MARTIN GM, AND MATTSON MP. Increased vulnerability of hippocampal neurons from presenilin-1 mutant knock-in mice to amyloid beta-peptide toxicity: central roles of superoxide production and caspase activation. *J Neurochem* 72: 1019–1029, 1999.
112. GUO Q, SOPHER BL, FURUKAWA K, PHAM DG, ROBINSON N, MARTIN GM, AND MATTSON MP. Alzheimer's presenilin mutation sensitizes neural cells to apoptosis induced by trophic factor withdrawal and amy-

loid beta-peptide: involvement of calcium and oxyradicals. *J Neurosci* 17: 4212–4222, 1997.
113. Guo Z, Ersoz A, Butterfield DA, and Mattson MP. Beneficial effects of dietary restriction on cerebral cortical synaptic terminals: preservation of glucose transport and mitochondrial function after exposure to amyloid β-peptide and oxidative and metabolic insults. *J Neurochem* 75: 314–320, 2000.
114. Guo Z, Kindy MS, Kruman I, and Mattson MP. ALS-linked Cu/Zn-SOD mutation impairs cerebral synaptic glucose and glutamate transport and exacerbates ischemic brain injury. *J Cereb Blood Flow Metab* 20: 463–468, 2000.
115. Guo ZH and Mattson MP. Neurotrophic factors protect synaptic terminals against amyloid- and oxidative stress-induced impairment of glucose transport, glutamate transport and mitochondrial function. *Cerebral Cortex* 10: 50–57, 1999.
116. Guo ZH and Mattson MP. In vivo 2-deoxyglucose administration preserves glucose and glutamate transport and mitochondrial function in cortical terminals after exposure to amyloid beta-peptide and iron: evidence for a stress response. *Exp Neurol* 166: 173–179, 2000.
117. Gurney ME, Cutting FB, Zhai P, Doble A, Taylor CP, Andrus PK, and Hall ED. Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial amyotrophic lateral sclerosis. *Ann Neurol* 39: 147–157, 1996.
118. Gurney ME, Pu H, Chiu AY, Dal Canto MC, Polchow CY, Alexander DD, Caliendo J, Hentati A, Kwon YW, and Deng HX. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. *Science* 264: 1772–1775, 1994.
119. Gutzmann H and Hadler D. Sustained efficacy and safety of idebenone in the treatment of Alzheimer's disease: update on a 2-year double-blind multicentre study. *J Neural Transm Suppl* 54: 301–310, 1998.
120. Hackam AS, Hodgson JG, Singaraja R, Zhang T, Gan L, Gutekunst CA, Hersch SM, and Hayden MR. Evidence for both the nucleus and cytoplasm as subcellular sites of pathogenesis in Huntington's disease in cell culture and in transgenic mice expressing mutant huntingtin. *Philos Trans R Soc Lond B Biol Sci* 354: 1047–1055, 1999.
121. Hamilton ML, Van Remmen H, Drake JA, Yang H, Guo ZM, Kewitt K, Walter CA, and Richardson A. Does oxidative damage to DNA increase with age? *Proc Natl Acad Sci USA* 98: 10469–10474, 2001.
122. Hardy J. Amyloid, the presenilins and Alzheimer's disease. *Trends Neurosci* 20: 154–159, 1997.
124. Haughey NJ, Liu D, Nath A, Borchard AC, and Mattson MP. Disruption of neurogenesis in the subventricular zone of adult mice, and in human cortical neuronal precursor cells in culture, by amyloid beta-peptide: implications for the pathogenesis of Alzheimer's disease. *Neuromol Med* 1: 125–136, 2002.
125. Hayashi M, Mistunaga F, Ohira K, and Shimizu K. Changes in BDNF-immunoreactive structures in the hippocampal formation of the aged macaque monkey. *Brain Res* 918: 191–196, 2001.
126. Heijmans BT, Westendorp RG, and Slagboom PE. Common gene variants, mortality and extreme longevity in humans. *Exp Gerontol* 35: 865–877, 2000.
127. Hendrie HC, Ogunniyi A, Hall KS, Baiyewu O, Unverzagt FW, Gureje O, Gao S, Evans RM, Ogunseyinde AO, Adeyinka AO, Musick B, and Hui SL. Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. *JAMA* 285: 739–747, 2001.
128. Hensley K, Carney JM, Mattson MP, Aksenova M, Harris M, Wu JF, Floyd R, and Butterfield DA. A model for β-amyloid aggregation and neurotoxicity based on free radical generation by the peptide: relevance to Alzheimer's disease. *Proc Natl Acad Sci USA* 91: 3270–3274, 1994.
129. Hodges S, Hertz N, Lockwood K, and Lister R. CoQ10: could it have a role in cancer management? *Biofactors* 9: 365–370, 1999.
130. Hodgson JG, Agopyan N, Gutekunst CA, Leavitt BR, Lepiane F, Singaraja R, Smith DJ, Bissada N, McCutcheon K, Nasir J, Jamot L, Li XJj, Stevens ME, Rosemond E, Roder JC, Phillips AG, Rubin EM, Hersch SM, and Hayden MR. A Yac mouse model for Huntington's disease with full-length mutant huntingtin, cytoplasmic toxicity, and selective striatal neurodegeneration. *Neuron* 23: 181–192, 1999.
131. Hoyer S. Age-related changes in cerebral oxidative metabolism. Implications for drug therapy. *Drugs Aging* 6: 210–218, 1995.
132. Hoyer S, Lannert H, Noldner M, and Chatterjee SS. Damaged neuronal energy metabolism and behavior are improved by Ginkgo biloba extract (EGb 761). *J Neural Transm* 106: 1171–1188, 1999.
133. Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, and Cole G. Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. *Science* 274: 99–102, 1996.
134. Huang X, Atwood CS, Hartshorn MA, Multhaup G, Goldstein LE, Scarpa RC, Cuajungco MP, Gray DN, Lim J, Moir RD, Tanzi RE, and Bush AI. The A beta peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. *Biochemistry* 38: 7609–7616, 1999.
135. Huh CS, Boulanger LM, Du H, Riquelme PA, Brotz TM, and Shatz CJ. Functional requirement for class I MHC in CNS development and plasticity. *Science* 290: 2155–2159, 2000.
136. Hull M, Lieb K, and Fiebich BL. Anti-inflammatory drugs: a hope for Alzheimer's disease? *Exp Opin Invest Drugs* 9: 671–683, 2000.
137. Huynh DP, Dy M, Nguyen D, Kiehl TR, and Pulst SM. Differential expression and tissue distribution of parkin isoforms during mouse development. *Dev Brain Res* 130: 173–181, 2001.
138. Ickes BR, Pham TM, Sanders LA, Albeck DS, Mohammed AH, and Granholm AC. Long-term environmental enrichment leads to regional increases in neurotrophin levels in rat brain. *Exp Neurol* 164: 45–52, 2000.
139. Ingram DK. Vaccine development for Alzheimer's disease: a shot of good news. *Trends Neurosci* 24: 305–307, 2001.
140. Ingram DK, Weindruch R, Spangler EL, and Freeman Walford RL Jr. Dietary restriction benefits learning and motor performance of aged mice. *J Gerontol* 42: 78–81, 1987.
141. Ip NY, Li Y, Yancopoulos GD, and Lindsay RM. Cultured hippocampal neurons show responses to BDNF, NT-3, and NT-4, but not NGF. *J Neurosci* 13: 3394–3405, 1993.
142. Ishida A, Furukawa K, Keller JN, and Mattson MP. Secreted form of beta-amyloid precursor protein shifts the frequency dependency for induction of LTD, and enhances LTP in hippocampal slices. *Neuroreport* 8: 2133–2137, 1997.
143. Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W, Augustin HJ, Dietze GJ, and Rett K. Oral administration of RAC-alpha-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial. *Free Radic Biol Med* 27: 309–314, 1999.
144. Jain KK. Evaluation of memantine for neuroprotection in dementia. *Exp Opin Invest Drugs* 9: 1397–1406, 2000.
145. Jana NR, Zemskov EA, Wang GH, and Nukina N. Altered proteasomal function due to the expression of polyglutamine-expanded truncated N-terminal huntingtin induces apoptosis by caspase activation through mitochondrial cytochrome *c* release. *Hum Mol Genet* 10: 1049–1059, 2001.
146. Jankowsky JL and Patterson PH. Cytokine and growth factor involvement in long-term potentiation. *Mol Cell Neurosci* 14: 273–286, 1999.
147. Jenner P and Olanow CW. Understanding cell death in Parkinson's disease. *Ann Neurol* 44: S72–S84, 1998.
148. Jensen PH, Li JY, Dahlstrom A, and Dotti CG. Axonal transport of synucleins is mediated by all rate components. *Eur J Neurosci* 11: 3369–3376, 1999.
149. Jick H, Zornberg GL, Jick SS, Seshadri S, and Drachman DA. Statins and the risk of dementia. *Lancet* 356: 27–1631, 2000.
150. Jin LW and Saitoh T. Changes in protein kinases in brain aging and Alzheimer's disease. Implications for drug therapy. *Drugs Aging* 6: 136–149, 1995.
151. Johansson BB. Functional outcome in rats transferred to an enriched environment 15 days after focal brain ischemia. *Stroke* 27: 324–326, 1996.
152. Jones TA, Chu CJ, Grande LA, and Gregory AD. Motor skills training enhances lesion-induced structural plasticity in the motor cortex of adult rats. *J Neurosci* 19: 10153–10163, 1999.
153. Jones TA, Klintsova AY, Kilman VL, Sirevaag AM, and Greenough WT. Induction of multiple synapses by experience in the visual cortex of adult rats. *Neurobiol Learn Mem* 68: 13–20, 1997.
154. Joseph JA, Shukitt-Hale B, Denisova NA, Bielinski D, Martin A, McEwen JJ, and Bickford PC. Reversals of age-related declines in

neuronal signal transduction, cognitive, and motor behavioral deficits with blueberry, spinach, or strawberry dietary supplementation. *J Neurosci* 19: 8114–8121, 1999.
155. KAEMMERER WF, RODRIGUEZ CM, STEER CJ, AND LOW WC. Creatine-supplemented diet extends Purkinje cell survival in spinocerebellar ataxia type 1 transgenic mice but does not prevent the ataxic phenotype. *Neuroscience* 103: 713–724, 2001.
156. KARAEV AL, SMIRNOVA TN, AND AVAKUMOV VM. The effect of ubiquinone Q_{10} and biotin on the growth and development of premature animals. *Eksp Klin Farmakol* 56: 55–57, 1993.
157. KATZMAN R. Apolipoprotein E and Alzheimer's disease. *Curr Opin Neurobiol* 4: 703–707, 1994.
158. KELLER JN, GEE J, AND DING Q. The proteasome in brain aging. *Aging Res Rev.* In press.
159. KELLER JN, GERMEYER A, BEGLEY JG, AND MATTSON MP. 17Beta-estradiol attenuates oxidative impairment of synaptic Na^+/K^+-ATPase activity, glucose transport, and glutamate transport induced by amyloid beta-peptide and iron. *J Neurosci Res* 50: 522–530, 1997.
160. KELLER JN, GUO Q, HOLTSBERG FW, BRUCE-KELLER AJ, AND MATTSON MP. 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.
161. KELLER JN, KINDY MS, HOLTSBERG FW, ST CLAIR DK, YEN HC, GERMEYER A, STEINER SM, BRUCE-KELLER AJ, HUTCHINS JB, AND MATTSON MP. 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.
162. KELLER JN, PANG Z, GEDDES JW, BEGLEY JG, GERMEYER A, WAEG G, AND MATTSON MP. Impairment of glucose and glutamate transport and induction of mitochondrial oxidative stress and dysfunction in synaptosomes by amyloid beta-peptide: role of the lipid peroxidation product 4-hydroxynonenal. *J Neurochem* 69: 273–284, 1997.
163. KELLY JF, FURUKAWA K, BARGER SW, RENGEN MR, MARK RJ, BLANC EM, ROTH GS, AND MATTSON MP. Amyloid beta-peptide disrupts carbachol-induced muscarinic cholinergic signal transduction in cortical neurons. *Proc Natl Acad Sci USA* 93: 6753–6758, 1996.
164. KEMPERMANN G, KUHN HG, AND GAGE FH. More hippocampal neurons in adult mice living in an enriched environment. *Nature* 386: 493–495, 1997.
165. KITADA T, ASAKAWA S, HATTORI N, MATSUMINE H, YAMAMURA Y, MINOSHIMA S, YOKOCHI M, MIZUNO Y, AND SHIMIZU N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 392: 605–608, 1998.
166. KLAPPER W, SHIN T, AND MATTSON MP. Differential regulation of telomerase activity and TERT expression during brain development in mice. *J Neurosci Res* 64: 252–260, 2001.
167. KLEIM JA, VIJ K, BALLARD DH, AND GREENOUGH WT. Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least four weeks. *J Neurosci* 17: 717–721, 1997.
168. KLIVENYI P, FERRANTE RJ, MATTHEWS RT, BOGDANOV MB, KLEIN AM, ANDREASSEN OA, MUELLER G, WERMER M, KADDURAH-DAOUK R, AND BEAL MF. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. *Nat Med* 5: 347–350, 1999.
169. KOLB B AND GIBB R. Environmental enrichment and cortical injury: behavioral and anatomical consequences of frontal cortex lesions. *Cereb Cortex* 1: 189–198, 1991.
170. KRUMAN II, CHAN SL, CULMSEE C, KRUMAN Y, PENIX L, AND MATTSON MP. Homocysteine elicits a DNA damage response in neurons resulting in apoptosis and hypersensitivity to excitotoxicity. *J Neurosci* 20: 6920–6926, 2000.
171. KRUMAN II, KUMARAVEL TS, LOHANI A, CUTLER RG, PEDERSEN WA, KRUMAN Y, EVANS M, AND MATTSON MP. Folic acid deficiency and homocysteine impair DNA repair and sensitize hippocampal neurons to death in experimental models of Alzheimer's disease. *J Neurosci* 22: 1752–1762, 2002.
172. KRUMAN II, PEDERSEN WA, SPRINGER JE, AND MATTSON MP. ALS-linked Cu/Zn-SOD mutation increases vulnerability of motor neurons to excitotoxicity by a mechanism involving increased oxidative stress and perturbed calcium homeostasis. *Exp Neurol* 160: 28–39, 1999.
173. KUBOVA H, FOLBERGROVA J, AND MARES P. Seizures induced by homocysteine in rats during ontogenesis. *Epilepsia* 36: 750–756, 1995.
174. KUHN HG, DICKINSON-ANSON H, AND GAGE FH. Neurogenesis in the dentate gyrus of the adult rat: age-related decrease of neuronal progenitor proliferation. *J Neurosci* 16: 2027–2033, 1996.
175. KUHN W, ROEBROEK R, BLOM H, VAN OPPENRAAIJ D, PRZUNTEK H, DRETCHNER A, BUTTNER T, WOITALLA D, AND MULLER T. Elevated plasma levels of homocysteine in Parkinson's disease. *Eur Neurol* 40: 225–227, 1998.
176. LANE MA. Nonhuman primate models in biogerontology. *Exp Gerontol* 35: 533–541, 2000.
176a. LANE MA, BLACK A, HAND YA, TILMONT EM, INGRAM DK, AND ROTH GS. Caloric restriction in primates. *Ann NY Acad Sci* 928: 287–295, 2001.
177. LANNFELT L, BOGDANOVIC N, APPELGREN H, AXELMAN K, LILIUS L, HANSSON G, SCHENK D, HARDY J, AND WINBLAD B. Amyloid precursor protein mutation causes Alzheimer's disease in a Swedish family. *Neurosci Lett* 168: 254–256, 1994.
178. LEBEL CP AND BONDY SC. Oxidative damage and cerebral aging. *Prog Neurobiol* 38: 601–609, 1992.
179. LEBOVITZ HE. Type 2 diabetes: an overview. *Clin Chem* 45: 1339–1345, 1999.
180. LEE CK, WEINDRUCH R, AND PROLLA TA. Gene-expression profile of the ageing brain in mice. *Nat Genet* 25: 294–297, 2000.
181. LEE IM, HENNEKENS CH, BERGER K, BURING JE, AND MANSON JE. Exercise and risk of stroke in male physicians. *Stroke* 30: 1–6, 1999.
182. LEE J, BRUCE-KELLER AJ, KRUMAN Y, CHAN SL, AND MATTSON MP. 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.
183. LEE J, DUAN W, LONG JM, INGRAM DK, AND MATTSON MP. Dietary restriction increases survival of newly-generated neural cells and induces BDNF expression in the dentate gyrus of rats. *J Mol Neurosci* 15: 99–108, 2000.
183a. LEE J, HERMAN JP, AND MATTSON MP. Dietary restriction selectively decreases glucocorticoid receptor expression in the hippocampus and cerebral cortex of rats. *Exp Neurol* 166: 435–441, 2000.
184. LEE J, SEROOGY K, AND MATTSON MP. Dietary restriction enhances neurotrophin signaling and neurogenesis in the hippocampus of adult mice. *J Neurochem* 80: 539–547, 2002.
185. LEE M, HYUN DH, HALLIWELL B, AND JENNER P. Effect of overexpression of wild-type and mutant Cu/Zn-superoxide dismutases on oxidative stress and cell death induced by hydrogen peroxide, 4-hydroxynonenal or serum deprivation: potentiation of injury by ALS-related mutant superoxide dismutases and protection by Bcl-2. *J Neurochem* 78: 209–220, 2001.
186. LEISSRING MA, AKBARI Y, FANGER CM, CAHALAN MD, MATTSON MP, AND LAFERLA FM. Capacitative calcium entry deficits and elevated luminal calcium content in mutant presenilin-1 knockin mice. *J Cell Biol* 149: 793–798, 2000.
187. LEVI F. Cancer prevention: epidemiology and perspectives. *Eur J Cancer* 35: 1912–1924, 1999.
188. LEVITT AJ AND KARLINSKY H. Folate, vitamin B_{12} and cognitive impairment in patients with Alzheimer's disease. *Acta Psychiatr Scand* 86: 301–305, 1992.
189. LI JC AND KAMINSKAS E. Deficient repair of DNA lesions in Alzheimer's disease fibroblasts. *Biochem Biophys Res Commun* 129: 733–738, 1985.
190. LI M, ONA VO, GUEGAN C, CHEN M, JACKSON-LEWIS V, ANDREWS LJ, OLSZEWSKI AJ, STIEG PE, LEE JP, PRZEDBORSKI S, AND FRIEDLANDER RM. Functional role of caspase-1 and caspase-3 in an ALS transgenic mouse model. *Science* 288: 335–339, 2000.
191. LI QX, EVIN G, SMALL DH, MULTHAUP G, BEYREUTHER K, AND MASTERS CL. Proteolytic processing of Alzheimer's disease beta A4 amyloid precursor protein in human platelets. *J Biol Chem* 270: 14140–14147, 1995.
192. LI SH, LAM S, CHENG AL, AND LI XJ. Intranuclear huntingtin increases the expression of caspase-1 and induces apoptosis. *Hum Mol Genet* 9: 2859–2867, 2000.
193. LITHGOW GJ AND ANDERSEN JK. The real Dorian Gray mouse. *Bioessays* 22: 410–413, 2000.
194. LIU J, SOLWAY K, MESSING RO, AND SHARP FR. Increased neurogenesis

in the dentate gyrus after transient global ischemia in gerbils. *J Neurosci* 18: 7768–7778, 1998.
195. LOGROSCINO G, MARDER COTE LK, TANG MX, SHEA S, AND MAYEUX R. Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. *Ann Neurol* 39: 89–94, 1996.
196. LOWE J. New pathological findings in amyotrophic lateral sclerosis. *J Neurol Sci* 124: 38–51, 1994.
197. LOWENSTEIN DH, CHAN PH, AND MILES MF. The stress protein response in cultured neurons: characterization and evidence for a protective role in excitotoxicity. *Neuron* 7: 1053–1060, 1991.
198. LU C, FU W, AND MATTSON MP. Telomerase protects developing neurons against DNA damage-induced cell death. *Dev Brain Res* 131: 167–171, 2001.
199. MACDONALD ME, AMBROSE CM, DUYAO MP, MYERS RH, LIN C, SRINIDHI L, AND BARNES G. A novel gene containing a trinucleotide repeat that is expanded and unstable on Hungtington's disease chromosomes. *Cell* 72: 971–983, 1993.
200. MAESAKA JK, WOLF-KLEIN G, PICCIONE JM, AND MA CM. Hypouricemia, abnormal renal tubular urate transport, and plasma natriuretic factor(s) in patients with Alzheimer's disease. *J Am Geriatr Soc* 41: 501–506, 1993.
201. MALBERG JE, EISCH AJ, NESTLER EJ, AND DUMAN RS. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* 20: 9104–9110, 2000.
202. MARGOLIS RL, O'HEARN E, ROSENBLATT A, WILLOUR V, HOLMES SE, FRANZ ML, CALLAHAN C, HWANG HS, TRONCOSO JC, AND ROSS CA. A disorder similar to Huntington's disease is associated with a novel CAG repeat expansion. *Ann Neurol* 50: 373–380, 2001.
203. MARINI AM, RABIN SJ, LIPSKY RH, AND MOCHETTI I. Activity-dependent release of brain-derived neurotrophic factor underlies the neuroprotective effect of *N*-methyl-D aspartate. *J Biol Chem* 273: 29394–29399, 1998.
204. MARK RJ, HENSLEY K, BUTTERFIELD DA, AND MATTSON MP. Amyloid beta-peptide impairs ion-motive ATPase activities: evidence for a role in loss of neuronal Ca^{2+} homeostasis and cell death. *J Neurosci* 15: 6239–6249, 1995.
205. MARK RJ, LOVELL MA, MARKESBERY WR, UCHIDA K, AND MATTSON MP. A role for 4-hydroxynonenal, an aldehydic product of lipid peroxidation, in disruption of ion homeostasis and neuronal death induced by amyloid beta-peptide. *J Neurochem* 68: 255–264, 1997.
206. MARK RJ, PANG Z, GEDDES JW, UCHIDA K, AND MATTSON MP. Amyloid beta-peptide impairs glucose transport in hippocampal and cortical neurons: involvement of membrane lipid peroxidation. *J Neurosci* 17: 1046–1054, 1997.
207. MARKESBERY WR, MONTINE TJ, AND LOVELL MA. Oxidative alterations in neurodegenerative diseases. In: *Pathogenesis of Neurodegenerative Disorders*, edited by Mattson MP. Totowa, NJ: Humana, 2001, p 21–51.
208. MARQUET A, BUI BT, AND FLORENTIN D. Biosynthesis of biotin and lipoic acid. *Vitam Horm* 61: 51–101, 2001.
209. MARTINEZ M, HERNANDEZ AI, AND MARTINEZ N. *N*-acetylcysteine delays age-associated memory impairment in mice: role in synaptic mitochondria. *Brain Res* 855: 100–106, 2000.
210. MASLIAH E, ROCKENSTEIN E, VEINBERGS I, MALLORY M, HASHIMOTO M, TAKEDA A, SAGARA Y, SISK A, AND MUCKE L. Dopaminergic loss and inclusion body formation in alpha-synuclein mice: implications for neurodegenerative disorders. *Science* 287: 1265–1269, 2000.
211. MATSUOKA Y, VILA M, LINCOLN S, MCCORMACK A, PICCIANO M, LAFRANCOIS J, YU X, DICKSON D, LANGSTON WJ, MCGOWAN E, FARRER M, HARDY J, DUFF K, PRZEDBORSKI S, AND DIMONTE DA. Lack of nigral pathology in transgenic mice expressing human alpha-synuclein driven by the tyrosine hydroxylase promoter. *Neurobiol Dis* 8: 535–539, 2001.
212. MATTHEWS RT, FERRANTE RJ, KLIVENYI P, YANG L, KLEIN AM, MUELLER G, KADDURAH-DAOUK R, AND BEAL MF. Creatine and cyclocreatine attenuate MPTP neurotoxicity. *Exp Neurol* 157: 142–149, 1999.
213. MATTSON MP. Cellular signaling mechanisms common to the development and degeneration of neuroarchitecture. A review. *Mech Ageing Dev* 50: 103–157, 1989.
214. MATTSON MP. Acetylcholine potentiates glutamate-induced neurodegeneration in cultured hippocampal neurons. *Brain Res* 497: 402–406, 1989.
215. MATTSON MP. Calcium as sculptor and destroyer of neural circuitry. *Exp Gerontol* 27: 29–49, 1992.
216. MATTSON MP. Cellular actions of beta-amyloid precursor protein and its soluble and fibrillogenic derivatives. *Physiol Rev* 77: 1081–1132, 1997.
217. MATTSON MP. Neuroprotective signal transduction: relevance to stroke. *Neurosci Biobehav Rev* 21: 193–206, 1997.
218. MATTSON MP. Modification of ion homeostasis by lipid peroxidation: roles in neuronal degeneration and adaptive plasticity. *Trends Neurosci* 21: 53–57, 1998.
219. MATTSON MP. Apoptosis in neurodegenerative disorders. *Nat Rev Mol Cell Biol* 1: 120–129, 2000.
220. MATTSON MP. Creatine: prescription for bad genes and a hostile environment? *Trends Neurosci* 23: 511, 2000.
221. MATTSON MP (Editor). *Telomerase, Aging and Disease*. Amsterdam: Elsevier, 2001.
221a. MATTSON MP (Editor). *Diet-Brain Connections*. Norwell, MA: Kluwer, 2002.
222. MATTSON MP. Brain evolution and lifespan regulation: conservation of signal transduction pathways that regulate energy metabolism. *Aging Res Rev*. In press.
223. MATTSON MP. Acomplices to neuronal death. *Nature* 415: 377–379, 2002.
224. MATTSON MP, BARGER SW, CHENG B, LIEBERBURG I, SMITH-SWINTOSKY VL, AND RYDEL RE. beta-Amyloid precursor protein metabolites and loss of neuronal Ca^{2+} homeostasis in Alzheimer's disease. *Trends Neurosci* 16: 409–414, 1993.
225. MATTSON MP AND CAMANDOLA S. NF-kappaB in neurodegenerative disorders. *J Clin Invest* 107: 247–254, 2001.
226. MATTSON MP, CHAN SL, AND CAMANDOLA S. Presenilin mutations and calcium signaling defects in the nervous and immune systems. *Bioessays* 23: 733–744, 2001.
227. MATTSON MP, CHENG B, DAVIS D, BRYANT K, LIEBERBURG I, AND RYDEL RE. beta-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity. *J Neurosci* 12: 376–389, 1992.
228. MATTSON MP AND DUAN W. "Apoptotic" biochemical cascades in synaptic compartments: roles in adaptive plasticity and neurodegenerative disorders. *J Neurosci Res* 58: 152–166, 1999.
229. MATTSON MP, GOODMAN Y, LUO H, FU W, AND FURUKAWA K. Activation of NF-κB protects hippocampal neurons against oxidative stress-induced apoptosis: evidence for induction of Mn-SOD and suppression of peroxynitrite production and protein tyrosine nitration. *J Neurosci Res* 49: 681–697, 1997.
230. MATTSON MP, GUO ZH, AND GEIGER JD. Secreted form of amyloid precursor protein enhances basal glucose and glutamate transport and protects against oxidative impairment of glucose and glutamate transport in synaptosomes by a cyclic GMP-mediated mechanism. *J Neurochem* 73: 532–537, 1999.
231. MATTSON MP AND KATER SB. Excitatory and inhibitory neurotransmitters in the generation and degeneration of hippocampal neuroarchitecture. *Brain Res* 478: 337–348, 1989.
232. MATTSON MP AND LINDVALL O. Neurotrophic factor and cytokine signaling in the aging brain. In: *The Aging Brain*, edited by Mattson MP and Geddes JW. Greenwich, CT: JAI, 1997, p. 299–345.
233. MATTSON MP, LOVELL MA, FURUKAWA K, AND MARKESBERY WR. Neurotrophic factors attenuate glutamate-induced accumulation of peroxides, elevation of $[Ca^{2+}]_i$ and neurotoxicity, and increase antioxidant enzyme activities in hippocampal neurons. *J Neurochem* 65: 1740–1751, 1995.
234. MATTSON MP, PARTIN J, AND BEGLEY JG. Amyloid beta-peptide induces apoptosis-related events in synapses and dendrites. *Brain Res* 807: 167–176, 1998.
235. MAYEUX R, COSTA R, BELL K, MERCHANT C, TUNG MX, AND JACOBS D. Reduced risk of Alzheimer's disease among individuals with low calorie intake. *Neurology* 59: S296–S297, 1999.
236. MAZZINI L, BALZARINI C, COLOMBO R, MORA G, PASTORE I, DE AMBROGIO R, AND CALIGARI M. Effects of creatine supplementation on exercise performance and muscular strength in amyotrophic lateral sclerosis: preliminary results. *J Neurol Sci* 191: 139–144, 2001.
237. MCCARTY MF. Versatile cytoprotective activity of lipoic acid may reflect its ability to activate signalling intermediates that trigger the

heat-shock and phase II responses. *Med Hypotheses* 57: 313–317, 2001.
238. McDonald JW, Liu XZ, Qu Y, Liu S, Mickey SK, Turetsky D, Gottlieb DI, and Choi DW. Transplanted embryonic stem cells survive, differentiate and promote recovery in injured rat spinal cord. *Nat Med* 5: 1410–1412, 1999.
239. McEwen BS. Effects of adverse experiences for brain structure and function. *Biol Psychiatry* 48: 721–731, 2000.
240. McGuffin P. The quantitative and molecular genetics of human intelligence. *Novartis Found Symp* 233: 243–255, 2000.
241. Mehler MF, Mabie PC, Zhu G, Gokhan S, and Kessler JA. Developmental changes in progenitor cell responsiveness to bone morphogenetic proteins differentially modulate progressive CNS lineage fate. *Dev Neurosci* 22: 74–85, 2000.
242. Mezey E and Chandross KJ. Bone marrow: a possible alternative source of cells in the adult nervous system. *Eur J Pharmacol* 405: 297–302, 2000.
243. Mohajeri MH, Filewicz DA, and Bohn MC. Intramuscular grafts of myoblasts genetically modified to secrete glial cell line-derived neurotrophic factor prevent motoneuron loss and disease progression in a mouse model of familial amyotrophic lateral sclerosis. *Hum Gene Ther* 10: 1853–1866, 1999.
244. Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, and Arendash GW. A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease. *Nature* 408: 982–985, 2000.
245. Morgan TE, Xie Z, Goldsmith S, Yoshida T, Lanzrein AS, Stone D, Rozovsky I, Perry G, Smith MA, and Finch CE. The mosaic of brain glial hyperactivity during normal ageing and its attenuation by food restriction. *Neuroscience* 89: 687–699, 1999.
246. Morrison BM, Hof PR, and Morrison JH. Determinants of neuronal vulnerability in neurodegenerative diseases. *Ann Neurol* 44: S32–S44, 1998.
247. Moulton PL, Boyko LN, Fitzpatrick JL, and Petros TV. The effect of Ginkgo biloba on memory in healthy male volunteers. *Physiol Behav* 73: 659–665, 2001.
248. Muller U and Krieglstein J. Prolonged pretreatment with alpha-lipoic acid protects cultured neurons against hypoxic, glutamate-, or iron-induced injury. *J Cereb Blood Flow Metab* 15: 624–630, 1995.
249. Munch G, Thome J, Foley P, Schinzel R, and Riederer P. Advanced glycation endproducts in ageing and Alzheimer's disease. *Brain Res Rev* 23: 134–143, 1997.
250. Murphy KP, Carter RJ, Lione LA, Mangiarini L, Mahal A, Bates GP, Dunnett SB, and Morton AJ. Abnormal synaptic plasticity and impaired spatial cognition in mice transgenic for exon 1 of the human Huntington's disease mutation. *J Neurosci* 20: 5115–5123, 2000.
250a. Nelson JF, Karelu SK, Bergman MD, and Felicio LS. Neuroendocrine involvement in aging: evidence from studies of reproductive aging and caloric restriction. *Neurobiol Aging* 16: 837–843, 1995.
251. Ness J, Sherman FT, and Pan CX. Alternative medicine: what the data say about common herbal therapies. *Geriatrics* 54: 33–38, 1999.
252. Neufeld EJ. Update on genetic risk factors for thrombosis and atherosclerotic vascular disease. *Hematol Oncol Clin North Am* 12: 1193–209, 1998.
253. Nilsberth C, Westlind-Danielsson A, Eckman CB, Condron MM, Axelman K, Forsell C, Stenh C, Luthman J, Teplow DB, Younkin SG, Naslund J, and Lannfelt L. The "Arctic" APP mutation (E693G) causes Alzheimer's disease by enhanced Abeta protofibril formation. *Nat Neurosci* 4: 887–893, 2001.
254. Nilsson M, Perfilieva E, Johansson U, Orwar O, and Eriksson P. Enriched environment increases neurogenesis in the adult rat dentate gyrus and improves spatial memory. *J Neurobiol* 39: 569–578, 1999.
254a. Nitta A, Ohmiya M, Sometani A, Itoh M, Nomoto H, Furukawa Y, and Furukawa S. Brain-derived neurotrophic factor prevents neuronal cell death induced by corticosterone. *J Neurosci Res* 57: 227–235, 1999.
255. Ohsawa I, Takamura C, Morrimoto T, Ishiguro M, and Kohsaka S. Amino-terminal region of secreted form of amyloid precursor protein stimulates proliferation of neural stem cells. *Eur J Neurosci* 11: 1907–1913, 1999.
256. O'Kusky Nasir J Jr, Cicchetti F, Parent A, and Hayden MR. Neuronal degeneration in the basal ganglia and loss of pallido-subthalamic synapses in mice with targeted disruption of the Huntington's disease gene. *Brain Res* 818: 468–479, 1999.
257. Ona VO, Vonsattel JP, Andrews LJ, Khan SQ, Chung WM, Frey AS, Menon AS, Li XJ, Stieg PE, Yuan J, Penney JB, Young AB, Cha JH, and Friedlander RM. Inhibition of caspase-1 slows disease progression in a mouse model of Huntington's disease. *Nature* 399: 263–267, 1999.
258. Oroth M and Schapira AH. Mitochondria and degenerative disorders. *Am J Med Genet* 106: 27–36, 2001.
259. Oster-Granite ML, Mcphie DL, Greenan J, and Neve RL. Age-dependent neuronal and synaptic degeneration in mice transgenic for the C terminus of the amyloid precursor protein. *J Neurosci* 16: 6732–6741, 1996.
260. Ozawa T. Genetic and functional changes in mitochondria associated with aging. *Physiol Rev* 77: 425–464, 1997.
261. Papaionnou N, Tooten PC, Van Ederen AM, Bohl Rofina J Jr, Tsangaris T, and Gruys E. Immunohistochemical investigation of the brain of aged dogs. I. Detection of neurofibrillary tangles and of 4-hydroxynonenal protein, an oxidative damage product, in senile plaques. *Amyloid* 8: 11–21, 2001.
262. Paradis E, Douillard H, Koutroumanis M, Goodyer C, and Leblanc A. Amyloid beta peptide of Alzheimer's disease downregulates Bcl-2 and upregulates bax expression in human neurons. *J Neurosci* 16: 7533–7539, 1996.
263. Parent A, Linden DJ, Sisodia SS, and Borchelt DR. Synaptic transmission and hippocampal long-term potentiation in transgenic mice expressing FAD-linked presenilin-1. *Neurobiol Dis* 6: 56–62, 1999.
264. Pasinelli P, Borchelt DR, Houseweart MK, Cleveland DW, and Brown RH. Caspase-1 is activated in neural cells and tissue with amyotrophic lateral sclerosis-associated mutations in copper-zinc superoxide dismutase. *Proc Natl Acad Sci USA* 95: 15763–15768, 1998.
265. Pedersen WA, Cashman NR, and Mattson MP. The lipid peroxidation product 4-hydroxynonenal impairs glutamate and glucose transport and choline acetyltransferase activity in NSC-19 motor neuron cells. *Exp Neurol* 155: 1–10, 1999.
266. Pedersen WA, Chan SL, and Mattson MP. A mechanism for the neuroprotective effect of apolipoprotein E: isoform-specific modification by the lipid peroxidation product 4-hydroxynonenal. *J Neurochem* 74: 1426–1433, 2000.
267. Pedersen WA, Culmsee C, Ziegler D, Herman JP, and Mattson MP. Aberrant stress response associated with severe hypoglycemia in a transgenic mouse model of Alzheimer's disease. *J Mol Neurosci* 13: 159–165, 1999.
268. Pedersen WA, Fu W, Keller JN, Markesbery WR, Appel S, Smith RG, Kasarskis E, and Mattson MP. Protein modification by the lipid peroxidation product 4-hydroxynonenal in the spinal cords of amyotrophic lateral sclerosis patients. *Ann Neurol* 44: 819–824, 1998.
269. Pedersen WA, Luo H, Kruman II, Kasarskis E, and Mattson MP. The prostate apoptosis response-4 protein participates in motor neuron degeneration in amyotrophic lateral sclerosis. *FASEB J* 14: 913–924, 2000.
270. Pedersen WA and Mattson MP. No benefit of dietary restriction on disease onset or progression in amyotrophic lateral sclerosis Cu/Zn-superoxide dismutase mutant mice. *Brain Res* 833: 117–120, 1999.
271. Pedersen WA, McCullers D, Culmsee C, Haughey N, Herman JP, and Mattson MP. Corticotropin-releasing hormone protects neurons against insults relevant to the pathogenesis of Alzheimer's disease. *Neurobiol Dis* 8: 492–503, 2001.
272. Pedersen WA, Wan R, Zhang P, and Mattson MP. Urocortin, but not urocortin II, protects cultured hippocampal neurons from cell death via activation of corticotropin-releasing hormone receptor type I. *J Neurosci* 22: 404–412, 2002.
273. Pereira C, Santos MS, and Oliveira C. Involvement of oxidative stress on the impairment of energy metabolism induced by A beta

peptides on PC12 cells: protection by antioxidants. *Neurobiol Dis* 6: 209–219, 1999.
274. PERLS T, TERRY DF, SILVER M, SHEA M, BOWEN J, JOYCE E, RIDGE SB, FRETTS R, DALY M, BREWSTER S, PUCA A, AND KUNKEL L. Centenarians and the genetics of longevity. *Results Probl Cell Differ* 29: 1–20, 2000.
275. PERRIG WJ, PERRIG P, AND STAHELIN HB. The relation between antioxidants and memory performance in the old and very old. *J Am Geriatr Soc* 45: 718–724, 1997.
276. PETRYNIAK MA, WURTMAN RJ, AND SLACK BE. Elevated intracellular calcium concentration increases secretory processing of the amyloid precursor protein by a tyrosine phosphorylation-dependent mechanism. *Biochem J* 320: 957–963, 1996.
277. PIEDRAHITA JA, OETAMA B, BENNETT GD, VAN WAES J, KAMEN BA, RICHARDSON J, LACEY SW, ANDERSON RG, AND FINNELL RH. Mice lacking the folic acid-binding protein Folbp1 are defective in early embryonic development. *Nat Genet* 23: 228–232, 1999.
278. PIKE CJ. Estrogen modulates neuronal Bcl-xL expression and beta-amyloid-induced apoptosis: relevance to Alzheimer's disease. *J Neurochem* 72: 1552–1563, 1999.
279. POGRIBNY IP, POIRRIER LA, AND JAMES SJ. Differential sensitivity to loss of cytosine methyl groups within the hepatic p53 gene of folate/methyl deficient rats. *Carcinogenesis* 16: 2863–2867, 1995.
280. POLYMEROPOULOS MH. Genetics of Parkinson's disease. *Ann NY Acad Sci* 920: 28–32, 2000.
281. POLYMEROPOULOS MH, LAVERDAN C, LEROY E, IDE SE, DEHEJIA A, DUTRA A, ROOT H, RUBENSTEIN J, BOYER R, STENROOS ES, CHANDRASEKHARAPPA S, ATHANASSIADOU A, PAPAPETROPOULOS T, JOHNSON WG, LAZZARINI AM, DUVOISIN RC, DI IORIO G, GOLBE LI, AND NUSSBAUM RL. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science* 276: 2045–2047, 1997.
282. PRASAD KN, COLE WC, HOVLAND AR, PRASAD KC, NAHREINI P, KUMAR B, EDWARDS-PRASAD J, AND ANDREATTA CP. Multiple antioxidants in the prevention and treatment of neurodegenerative disease: analysis of biologic rationale. *Curr Opin Neurol* 12: 761–770, 1999.
283. PREHN JH, KARKOUTLY C, NUBLISCH J, PERUCHE B, AND KRIEGLSTEIN J. Dihydrolipoate reduces neuronal injury after cerebral ischemia. *J Cereb Blood Flow Metab* 12: 78–87, 1992.
284. QUERFURTH HW, JIANG J, GEIGER JD, AND SELKOE DJ. Caffeine stimulates amyloid beta-peptide release from beta-amyloid precursor protein-transfected HEK293 cells. *J Neurochem* 69: 1580–1591, 1997.
285. RADAK Z, KANEKO T, TAHARA S, NAKAMOTO H, PUCSOK J, SASVARI M, NYAKAS C, AND GOTO S. Regular exercise improves cognitive function and decreases oxidative damage in rat brain. *Neurochem Int* 38: 17–23, 2001.
286. RALL SC AND MAHLEY RW. The role of apolipoprotein E genetic variants in lipoprotein disorders. *J Intern Med* 231: 653–659, 1992.
287. RAMASSAMY C, CLOSTRE F, CHRISTEN Y, AND COSTENTIN J. Prevention by a Ginkgo biloba extract (GBE 761) of the dopaminergic neurotoxicity of MPTP. *J Pharm Pharmacol* 42: 785–789, 1990.
288. RAMI A AND KRIEGLSTEIN J. Muscarinic-receptor antagonist scopolamine rescues hippocampal neurons from death induced by glutamate. *Brain Res* 788: 323–326, 1998.
289. RANCHON I, GORRAND JM, CLUZEL J, DROY-LEFAIX MT, AND DOLY M. Functional protection of photoreceptors from light-induced damage by dimethylthiourea and Ginkgo biloba extract. *Invest Ophthalmol Vis Sci* 40: 1191–1199, 1999.
290. RAO AV AND AGARWAL S. Role of antioxidant lycopene in cancer and heart disease. *J Am Coll Nutr* 19: 563–569, 2000.
291. RAO MS AND MATTSON MP. Stem cells and aging: expanding the possibilities. *Mech Ageing Dev* 122: 713–734, 2001.
292. RAVAGLIA G, FORTI P, MAIOLI F, VETTORI C, GROSSI G, BARGOSSI AM, CALDARERA M, FRANCESCHI C, FACCHINI A, MARIANI E, AND CAVALLI G. Elevated plasma homocysteine levels in centenarians are not associated with cognitive impairment. *Mech Ageing Dev* 121: 251–261, 2000.
293. RAVAGNAN L, GURBUXANI S, SUSIN SA, MAISSE C, DAUGAS E, ZAMZAMI N, MAK T, JAATTELA M, PENNINGER JM, GARRIDO C, AND KROEMER G. Heat-shock protein 70 antagonizes apoptosis-inducing factor. *Nat Cell Biol* 3: 839–843, 2001.
294. REDDY PH, WILLIAMS M, CHARLES V, GARRETT L, PIKE-BUCHANAN L, WHETSELL WO, MILLER G, AND TAGLE DA. Behavioural abnormalities and selective neuronal loss in HD transgenic mice expressing mutated full-length HD cDNA. *Nat Genet* 20: 198–202, 1998.
295. RISSANEN TH, VOUTILAINEN S, NYYSSONEN K, LAKKA TA, SIVENIUS J, SALONEN R, KAPLAN GA, AND SALONEN JT. Low serum lycopene concentration is associated with an excess incidence of acute coronary events and stroke: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Br J Nutr* 85: 749–754, 2001.
296. RITCHIE PD, CAMERON PA, UGONI AM, AND KAYE AH. A study of the functional outcome and mortality in elderly patients with head injuries. *J Clin Neurosci* 7: 301–304, 2000.
297. ROBISON SH, MUNZER JS, TANDAN R, AND BRADLEY WG. Alzheimer's disease cells exhibit defective repair of alkylating agent-induced DNA damage. *Ann Neurol* 21: 250–258, 1987.
298. ROEDTER A, WINKLER C, SAMII M, WALTER GF, BRANDIS A, AND NIKKHAH G. Comparison of unilateral and bilateral intrastriatal 6-hydroxydopamine-induced axon terminal lesions: evidence for interhemispheric functional coupling of the two nigrostriatal pathways. *J Comp Neurol* 432: 217–229, 2000.
299. ROGHANI M AND BEHZADI G. Neuroprotective effect of vitamin E on the early model of Parkinson's disease in rat: behavioral and histochemical evidence. *Brain Res* 892: 211–217, 2001.
300. ROJAS-FERNANDEZ CH, LANCTOT KL, ALLEN DD, AND MACKNIGHT C. Pharmacotherapy of behavioral and psychological symptoms of dementia: time for a different paradigm? *Pharmacotherapy* 21: 74–102, 2001.
301. ROMAN GC. Neuroepidemiology of amyotrophic lateral sclerosis: clues to aetiology and pathogenesis. *J Neurol Neurosurg Psychiatry* 61: 131–137, 1996.
302. ROSEN DR, SIDDIQUE T, PATTERSON D, FIGLEWICZ DA, SAPP P, HENTATI A, AND DONALDSON D. Mutations in Cu/Zn superoxide dismuase gene are associated with familial amyotrophic lateral sclerosis. *Nature* 362: 59–62, 1993.
303. ROTH GS AND JOSEPH JA. Cellular and molecular mechanisms of impaired dopaminergic function during aging. *Ann NY Acad Sci* 719: 129–135, 1994.
304. RUSSO-NEUSTADT A, BEARD RC, AND COTMAN CW. Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. *Neuropsychopharmacology* 21: 679–682, 1999.
305. SAHA AR, NINKINA NN, HANGER DP, ANDERTON BH, DAVIES AM, AND BUCHMAN VL. Induction of neuronal death by alpha-synuclein. *Eur J Neurosci* 12: 3073–3077, 2000.
306. SAITO S, KOBAYASHI S, OHASHI Y, IGARASHI M, KOMIYA Y, AND ANDO S. Decreased synaptic density in aged brains and its prevention by rearing under enriched environment as revealed by synaptophysin contents. *J Neurosci Res* 39: 57–62, 1994.
306a. SAPOLSKY RM. Glucocorticoids, stress, and their adverse neurological effects: relevance to aging. *Exp Neurol* 34: 721–732, 1999.
306b. SCHAPIRA AH. Mitochondrial involvement in Parkinson's disease, Huntington's disease, hereditary spastic paraplegia and Friedreich's ataxia. *Biochim Biophys Acta* 1410: 159–170, 1999.
307. SCHEFF SW AND PRICE DA. Synaptic density in the inner molecular layer of the hippocampal dentate gyrus in Alzheimer disease. *J Neuropathol Exp Neurol* 57: 1146–1153, 1998.
308. SCHEFF SW, PRICE DA, AND SPARKS DL. Quantitative assessment of possible age-related change in synaptic numbers in the human frontal cortex. *Neurobiol Aging* 22: 355–365, 2001.
309. SCHEFF SW, SCOTT SA, AND DEKOSKY ST. Quantitation of synaptic density in the septal nuclei of young and aged Fischer 344 rats. *Neurobiol Aging* 12: 3–12, 1991.
310. SCHENK D, BARBOUR R, DUNN W, GORDON G, GRAJEDA H, GUIDO T, HU K, HUANG J, JOHNSON-WOOD K, KHAN K, KHOLODENKO D, LEE M, LIAO Z, LIEBERBURG I, MOTTER R, MUTTER L, SORIANO F, SHOPP G, VASQUEZ N, VANDEVERT C, WALKER S, WOGULIS M, YEDNOCK T, GAMES D, AND SEUBERT P. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 400: 173–177, 1999.
311. SCHILLING G, JINNAH HA, GONZALES V, COONFIELD ML, KIM Y, WOOD JD, PRICE DL, LI XJ, JENKINS N, COPELAND N, MORAN T, ROSS CA, AND BORCHELT DR. Distinct behavioral and neuropathological abnormalities in transgenic mouse models of HD and DRPLA. *Neurobiol Dis* 8: 405–418, 2001.
312. SCHWAB ME. Regenerative nerve fiber growth in the adult central nervous system. *News Physiol Sci* 13: 294–298, 1998.

313. Schwaninger M, Ringleb P, Winter R, Kohl B, Fiehn W, Rieser PA, and Walter-Sack I. Elevated plasma concentrations of homocysteine in antiepileptic drug treatment. *Epilepsia* 40: 345–350, 1999.
314. Scott JM and Weir DG. Folic acid, homocysteine and one-carbon methabolism: a review of the essential biochemistry. *J Cardiovasc Risk* 5: 223–227, 1998.
315. Selhub J, Bagley LC, Miller J, and Rosenberg IH. B vitamins, homocysteine, and neurocognitive function in the elderly. *Am J Clin Nutr* 71: 614S–620S, 2000.
316. Sennvik K, Benedikz E, Fasthom J, Sundstrom E, Winblad B, and Ankarcrona M. Calcium ionophore A23187 specifically decreases the secretion of beta-secretase cleaved amyloid precursor protein during apoptosis in primary rat cortical cultures. *J Neurosci Res* 63: 429–437, 2001.
317. Shay KA and Roth DL. Association between aerobic fitness and visuospatial performance in healthy older adults. *Psychol Aging* 7: 15–24, 1992.
318. Shepherd JE. Effects of estrogen on congnition mood, and degenerative brain diseases. *J Am Pharm Assoc* 41: 221–228, 2001.
319. Shields DC, Kirke PN, Mills JL, Ramsbottom D, Molloy AM, Burke H, Weir DG, Scott JM, and Whitehead AS. The "thermolabile" variant of methylenetetrahydrofolate reductase and neural tube defects: an evaluation of genetic risk and the relative importance of the genotypes of the embryo and the mother. *Am J Hum Genet* 64: 1045–1055, 1999.
320. Shimura H, Hattori N, Kubo SI, Mizuno Y, Asakawa S, Minoshima S, Shimizu N, Iwai K, Chiba T, Tanaka K, and Suzuki T. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase. *Nat Genet* 25: 302–305, 2000.
321. Shimura H, Schlossmacher MG, Hattori N, Frosch MP, Trockenbacher A, Schneider R, Mizuno Y, Kosik KS, and Selkoe DJ. Ubiquitination of a new form of alpha-synuclein by parkin from human brain: implications for Parkinson's disease. *Science* 293: 263–269, 2001.
322. Shors TJ, Miesegaes G, Beylin A, Zhao M, Rydel T, and Gould E. Neurogenesis in the adult is involved in the formation of trace memories. *Nature* 410: 372–376, 2001.
323. Sinden JD, Stroemer P, Grigoryan G, Patel S, French SJ, and Hodges H. Functional repair with neural stem cells. *Novartis Found Symp* 231: 270–283, 2000.
324. Singh RB, Wander GS, Rstogi A, Shukla PK, Mittal A, Sharma JP, Mehrotra SK, Kapoor R, and Chopra RK. Randomized, double-blind placebo-controlled trial of coenzyme Q_{10} in patients with acute myocardial infarction. *Cardiovasc Drugs Ther* 12: 347–353, 1998.
325. Sirotnak FM Tolner B. Carrier-mediated membrane transport of folates in mammalian cells. *Annu Rev Nutr* 19: 91–122, 1999.
326. Sloane JA, Hollander W, Moss MB, Rosene DL, and Abraham CR. Increased microglial activation and protein nitration in white matter of the aging monkey. *Neurobiol Aging* 20: 395–405, 1999.
327. Smith JD. Apolipoprotein E_4: an allele associated with many diseases. *Ann Med* 32: 118–127, 2000.
327a. Smith MA, Makin OS, Kvetnansk YR, and Post RM. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. *J Neurosci* 15: 1768–1777, 1995.
328. Smithells RW, Sheppard S, and Schorah CJ. Vitamin dificiencies and neural tube defects. *Arch Dis Child* 51: 944–950, 1976.
329. Snowdon DA, Kemper SJ, Mortimer JA, Greiner LH, Wekstein DR, and Markesbery WR. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life. Findings from the Nun Study. *JAMA* 275: 528–532, 1996.
330. Socci DJ, Crandall BM, and Arendash GW. Chronic antioxidant treatment improves the cognitive performance of aged rats. *Brain Res* 693: 88–94, 1995.
331. Sohal RS, Agarwal S, Candas M, Forster MJ, and Lal H. Effect of age and caloric restriction on DNA oxidative damage in different tissues of C57BL/6 mice. *Mech Ageing Dev* 76: 215–224, 1994.
332. Sonntag WE, Lynch C, Thornton P, Khan A, Bennett S, and Ingram R. The effects of growth hormone and IGF-I deficiency on cerebrovascular and brain ageing. *J Anat* 197: 575–585, 2000.
333. Sousa N, Lukoyanov NV, Madeira MD, Almeida OF, and Paula-Barbosa MM. Reorganization of the morphology of hippocampal neurites and synapses after stress-induced damage correlates with behavioral improvement. *Neuroscience* 97: 253–266, 2000.
334. Soutar AK. Familial hypercholesterolaemia and LDL receptor mutations. *J Intern Med* 231: 633–641, 1992.
335. Spencer PS, Kisby GE, Ross SM, Roy DN, Hugon J, Ludolph AC, and Nunn PB. Guam ALS-PDC: possible causes. *Science* 262: 825–826, 1993.
336. Stewart J, Mitchell J, and Kalant N. The effects of life-long food restriction on spatial memory in young and aged Fischer 344 rats measured in the eight-arm radial and the Morris water mazes. *Neurobiol Aging* 10: 669–675, 1989.
337. St. George-Hyslop PH. Genetic factors in the genesis of Alzheimer's disease. *Ann NY Acad Sci* 924: 1–7, 2000.
338. Sullivan PG, Geiger JD, Mattson MP, and Scheff SW. Dietary supplement creatine protects against traumatic brain injury. *Ann Neurol* 48: 723–729, 2000.
339. Sun Y, Nadal-Vicens M, Misono S, Lin MZ, Zubiaga A, Hua X, Fan G, and Greenberg ME. Neurogenin promotes neurogenesis and inhibits glial differentiation by independent mechanisms. *Cell* 104: 365–376, 2001.
340. Surtees R, Bowron A, and Leonard J. Cerebrospinal fluid and plasma total homocysteine and related metabolites in children with cystathionine beta-synthase deficiency: the effect of treatment. *Pediatr Res* 42: 577–582, 1997.
341. Sze JY, Victor M, Loer C, Shi Y, and Ruvkun G. Food and metabolic signalling defects in a *Caenorhabditis elegans* serotonin-synthesis mutant. *Nature* 403: 560–564, 2000.
342. Tabrizi SJ, Orth M, Wilkinson JM, Taanman JW, Warner TT, Cooper JM, and Schapira AH. Expression of mutant alpha-synuclein causes increased susceptibility to dopamine toxicity. *Hum Mol Genet* 9: 2683–2689, 2000.
343. Tanaka Y, Engelender S, Igarashi S, Rao RK, Wanner T, Tanzi RE, Sawa AL, Dawson V, Dawson TM, and Ross CA. Inducible expression of mutant alpha-synuclein decreases proteasome activity and increases sensitivity to mitochondria-dependent apoptosis. *Hum Mol Genet* 10: 919–926, 2001.
344. Tanigaki K, Nogaki F, Takahashi J, Tashiro K, Kurooka H, and Honjo T. Notch1 and Notch3 instructively restrict bFGF-responsive multipotent neural progenitor cells to an astroglial fate. *Neuron* 29: 45–55, 2001.
345. Tohgi H, Abe T, Takahashi S, and Kikuchi T. The urate and xanthine concentrations in the cerebrospinal fluid in patients with vascular dementia of the Binswanger type, Alzheimer type dementia, and Parkinson's disease. *J Neural Transm Park Dis Dement Sect* 6: 119–126, 1993.
346. Turmaine M, Raza A, Mahal A, Mangiarini L, Bates GP, and Davies SW. Nonapoptotic neurodegeneration in a transgenic mouse model of Huntington's disease. *Proc Natl Acad Sci USA* 97: 8093–8097, 2000.
347. Turnbull S, Tabner BJ, El-Agnaf OM, Moore S, Davies Y, and Allsop D. α-Synuclein implicated in Parkinson's disease catalyses the formation of hydrogen peroxide in vitro. *Free Radic Biol Med* 30: 1163–1170, 2001.
348. Uauy R, Peirano P, Hoffman D, Mena P, Birch D, and Birch E. Role of essential fatty acids in the function of the developing nervous system. *Lipids* 31: S167–S176, 1996.
349. Van Boxtel MP, Paas FG, Houx PJ, Adam JJ, Teeken JC, and Jolles J. Aerobic capacity and cognitive performance in a cross-sectional aging study. *Med Sci Sports Exercise* 29: 1357–1365, 1997.
350. Van Dongen MC, Van Rossum E, Kessels AG, Sielhorst HJ, and Knipschild PG. The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: new results of a randomized clinical trial. *J Am Geriatr Soc* 48: 1183–1194, 2000.
351. Van Praag H, Kempermann G, and Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nat Neurosci* 2: 266–270, 1999.
352. Van Rijzingen IM, Gispen WH, and Spruijt BM. Postoperative environmental enrichment attenuates fimbria-fornix lesion-induced impairments in Morris maze performance. *Neurobiol Learn Mem* 67: 21–28, 1997.
353. Varadarajan S, Yatin S, Kanski J, Jahanshahi F, and Butterfield DA. Methionine residue 35 is important in amyloid beta-peptide-associated free radical oxidative stress. *Brain Res Bull* 50: 133–141, 1999.

354. VATASSERY GT, BAUER T, AND DYSKEN M. High doses of vitamin E in the treatment of disorders of the central nervous system in the aged. *Am J Clin Nutr* 70: 793–801, 1999.
355. VAUGHAN DAVIS MB AND WOOD NW JR. Genetics of Parkinsonism: a review. *Ann Hum Genet* 65: 111–126, 2001.
356. VELDMAN BA, WIJN AM, KNOERS N, PRAAMSTRA P, AND HORSTINK MW. Genetic and environmental risk factors in Parkinson's disease. *Clin Neurol Neurosurg* 100: 15–26, 1998.
357. VOLLES MJ, LEE SJ, ROCHET JC, SHTILERMAN MD, DING TT, KESSLER JC, AND LANSBURY PT. Vesicle permeabilization by protofibrillar alpha-synuclein: implications for the pathogenesis and treatment of Parkinson's disease. *Biochemistry* 40: 7812–7819, 2001.
358. VUKOSAVIC S, STEFANIS L, JACKSON-LEWIS V, GUEGAN C, ROMERO N, CHEN C, DUBOIS-DAUPHIN M, AND PRZEDBORSKI S. Delaying caspase activation by Bcl-2: a clue to disease retardation in a transgenic mouse model of amyotrophic lateral sclerosis. *J Neurosci* 20: 9119–9125, 2000.
359. WAINFAN E AND POIRIER LA. Methyl groups in carcinogenesis: effects on DNA methylation and gene expression. *Cancer Res* 52: 2068–2077, 1992.
360. WALTON M, HENDERSON C, MASON-PARKER S, LAWLOR P, ABRAHAM WC, BILKEY D, AND DRAGUNOW M. Immediate early gene transcription and synaptic modulation. *J Neurosci Res* 58: 96–106, 1999.
361. WANG GT, LADROR US, HOLZMAN TF, KLEIN WL, AND KRAFFT GA. Cleavage of fluorogenic substrates for APP-processing proteases by human brain extracts. Ca^{2+}-substrate interaction is responsible for Ca^{2+} stimulation of the neural protease activity. *Mol Chem Neuropathol* 23: 191–199, 1994.
362. WEINDRUCH R AND SOHAL RS. Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. *N Engl J Med* 337: 986–994, 1997.
363. WESNERS KA, WARD T, MCGINTY A, AND PETRINI O. The memory enhancing effects of a Ginkgo biloba/Panax ginseng combination in healthy middle-aged volunteers. *Psychopharmacology* 152: 353–361, 2000.
364. WIESE S, DIGBY MR, GUNNERSEN JM, GOTZ R, PEI G, HOLTMANN B, LOWENTHAL J, AND SENDTNER M. The anti-apoptotic protein ITA is essential for NGF-mediated survival of embryonic chick neurons. *Nat Neurosci* 2: 978–983, 1999.
365. WILLIAMSON TL, BRUIJN LI, ZHU Q, ANDERSON KL, ANDERSON SD, JULIEN JP, AND CLEVELAND DW. Absence of neurofilaments reduces the selective vulnerability of motor neurons and slows disease caused by a familial amyotrophic lateral sclerosis-linked superoxide dismutase 1 mutant. *Proc Natl Acad Sci USA* 95: 9631–9636, 1998.
366. WOLKOW CA, KIMURA KD, LEE MS, AND RUVKUN G. Regulation of *C. elegans* life-span by insulinlike signaling in the nervous system. *Science* 290: 147–150, 2000.
367. WOLOZIN B, IWASAKI K, VITO P, GANJEI JK, LACANA E, SUNDERLAND T, ZHAO B, KUSIAK JW, WASCO W, AND D'ADAMIO L. Participation of presenilin 2 in apoptosis: enhanced basal activity conferred by an Alzheimer mutation. *Science* 274: 1710–1713, 1996.
368. WONG PC, PARDO CA, BORCHELT DR, LEE MK, COPELAND NG, JENKINS NA, SISODIA SS, CLEVELAND DW, AND PRICE DL. An adverse property of a familial ALS-linked SOD1 mutation causes motor neuron disease characterized by vacuolar degeneration of mitochondria. *Neuron* 14: 1105–1116, 1995.
369. XIA W, OSTASZEWSKI BL, KIMBERLY WT, RAHMATI T, MOORE CL, WOLFE MS, AND SELKOE DJ. Fad mutations in presenilin-1 or amyloid precursor protein decrease the efficacy of a gamma-secretase inhibitor: evidence for direct involvement of PS1 in the gamma-secretase cleavage complex. *Neurobiol Dis* 7: 673–681, 2000.
370. XIE Z AND SASTRY BR. Induction of hippocampal long-term potentiation by alpha-tocopherol. *Brain Res* 604: 173–179, 1993.
371. YAMADA K, TANAKA T, HAN D, SENZAKI K, KAMEYAMA T, AND NABESHIMA T. Protective effects of idebenone and alpha-tocopherol on beta-amyloid-(1—42)-induced learning and memory deficits in rats: implication of oxidative stress in beta-amyloid-induced neurotoxicity in vivo. *Eur J Neurosci* 11: 83–90, 1999.
372. YANDAVA BD, BILLINGHURST LL, AND SNYDER EY. "Global" cell replacement is feasible via neural stem cell transplantation: evidence from the dysmyelinated shiverer mouse brain. *Proc Natl Acad Sci USA* 96: 7029–7034, 1999.
373. YAO Z, DRIEU K, AND PAPADOPOULOS V. The Ginkgo biloba extract EGb 761 rescues the PC12 neuronal cells from beta-amyloid-induced cell death by inhibiting the formation of beta amyloid-derived diffusible neurotoxic ligands. *Brain Res* 889: 181–190, 2001.
374. YASUI K, KOWA H, NAKASO K, TAKESHIMA T, AND NAKASHIMA K. Plasma homocysteine and MTHFR C677T genotype in levodopa-treated patients with PD. *Neurology* 55: 437–440, 2000.
375. YOO AS, CHENG I, CHUNG S, GRENFELL TZ, LEE H, PACK-CHUNG E, HANDLER M, SHEN J, XIA W, TESCO G, SAUNDERS AJ, DING K, FROSCH MP, TANZI RE, AND KIM TW. Presenilin-mediated modulation of capacitative calcium entry. *Neuron* 27: 561–572, 2000.
376. YOSHINO Y. Possible involvement of folate cycle in the pathogenesis of amyotrophic lateral sclerosis. *Neurochem Res* 9: 387–391, 1984.
377. YOUNG D, LAWLOR PA, LEONE P, DRAGUNOW M, AND DURING MJ. Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nat Med* 5: 448–453, 1999.
378. YU ZF, BRUCE-KELLER AJ, GOODMAN Y, AND MATTSON MP. Uric acid protects neurons against excitotoxic and metabolic insults in cell culture, and against focal ischemic brain injury in vivo. *J Neurosci Res* 53: 613–625, 1998.
379. YU ZF, LUO H, FU W, AND MATTSON MP. The endoplasmic reticulum stress-responsive protein GRP78 protects neurons against excitotoxicity and apoptosis: suppression of oxidative stress and stabilization of calcium homeostasis. *Exp Neurol* 155: 302–314, 1999.
380. YU ZF AND MATTSON MP. 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.
381. YUREK DM AND FLETCHER-TURNER A. Differential expression of GDNF, BDNF, and NT-3 in the aging nigrostriatal system following a neurotoxic lesion. *Brain Res* 891: 228–235, 2001.
382. ZHAN SS, BEYREUTHER K, AND SCHMITT HP. Quantitative assessment of the synaptophysin immuno-reactivity of the cortical neuropil in various neurodegenerative disorders with dementia. *Dementia* 4: 66–74, 1993.
383. ZHANG B, TU P, ABTAHIAN F, TROJANOWSKI JQ, AND LEE VM. 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.
384. ZHANG L, XING G, BARKER JL, CHANG Y, MARIC D, MA W, LI B, AND RUBINOW DR. α-Lipoic acid protects rat cortical neurons against cell death induced by amyloid and hydrogen peroxide through the Akt signalling pathway. *Neurosci Lett* 312: 125–128, 2001.
386. ZHANG Y, TATSUNO T, CARNEY JM, AND MATTSON MP. Basic FGF, NGF, and IGFs protect hippocampal and cortical neurons against iron-induced degeneration. *J Cereb Blood Flow Metab* 13: 378–388, 1993.
387. ZHU H, FU W, AND MATTSON MP. The catalytic subunit of telomerase protects neurons against amyloid beta-peptide-induced apoptosis. *J Neurochem* 75: 117–124, 2000.
388. ZHU H, GUO Q, AND MATTSON MP. Dietary restriction protects hippocampal neurons against the death-promoting action of a presenilin-1 mutation. *Brain Res* 842: 224–229, 1999.
389. ZOGHBI HY AND ORR HT. Glutamine repeats and neurodegeneration. *Annu Rev Neurosci* 23: 217–247, 2000.
390. ZUCCATO C, CIAMMOLA A, RIGAMONTI D, LEAVITT BR GOFFREDO D, CONTI L, MACDONALD ME, FRIEDLANDER RM, SILANI V, HAYDEN MR, TIMMUSK T, SIPIONE S, AND CATTANEO E. Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. *Science* 293: 493–498, 2001.