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Recruiting Adaptive Cellular Stress Responses for Successful Brain Aging

Alexis M. Stranahan[1] and **Mark P. Mattson**[2,*]

[1]Physiology Department, Georgia Health Sciences University, Augusta, GA, USA

[2]Laboratory of Neurosciences, National Institute on Aging Intramural Research Program, National Institutes of Health, Baltimore, MD, USA

Abstract

Successful aging is determined in part by genetic background, but also by experiential factors associated with lifestyle and culture. Dietary, behavioral and pharmacological interventions have been identified as potential means to slow brain aging and forestall neurodegenerative disease. Many of these interventions recruit adaptive cellular stress responses to strengthen neuronal networks and enhance plasticity. In this Perspective, we describe several determinants of healthy and pathological brain aging, with insights into how these processes are accelerated or prevented. We also describe the mechanisms underlying the neuroprotective actions of exercise and nutritional interventions, with the goal of recruiting these molecular targets for the treatment and prevention of neurodegenerative disease.

Introduction

Aging is associated with numerous physiological alterations across multiple organ systems, including the brain. Central nervous system (CNS) consequences of aging occur in part due to intrinsic responses to accumulated ‘wear and tear’, but may also be secondary to aging in other organ systems, including reproductive aging[1] (Behl, 2002) and muscle loss[2] (Burns et al., 2010). Some changes that occur in the context of aging are adaptive. For example, despite increased physical ailments, the elderly self-report higher levels of happiness relative to middle-aged and younger populations[3], and presumably, the increased rate of contentment in older adults has some neuronal correlate. Other age-related alterations, such as declining executive function and motor impairment, are more pernicious; ideally, these changes could be delayed or prevented by targeted CNS interventions. Many of these interventions, including exercise and dietary moderation, resemble the dictates of common sense. In this article we describe mechanisms underlying neuroprotective ‘common sense’ manipulations, with the goal of harnessing these mechanisms to protect against the deleterious consequences of brain aging.

[*]Corresponding Author. Mark P. Mattson, Ph.D., Laboratory of Neurosciences, Biomedical Research Center, 05C214, 251 Bayview Boulevard, Baltimore, MD 21224-6825, Phone: 410-558-8463. Fax: 410-558-8465, mattsonm@grc.nia.nih.gov.

Salient features of brain aging

The aging process leads to an increase in the variability associated with cognitive and motor capabilities in humans[4], and rodent models[5]. Just as some humans maintain cognitive function into their eighth decade and beyond, a subset of aged rodents retains the capacity for performance across a range of cognitive tasks[5–7]. In this regard, it is possible to distinguish between healthy aging with preserved cognition, age-related cognitive impairment, and neuropathology (Figure 1). As described in the remaining sections of this article, these general functional features of brain aging are underlain by impaired adaptive cellular stress responses, defined as the ability of neurons to rebound from potentially damaging alterations of the local environment and the endocrine milieu.

Regardless of genetic background, there are several major cellular and molecular changes that occur in the CNS during normal aging that are shared, more-or-less, with age-related alterations in other organ systems. These fundamental aspects of brain aging, common across the spectrum of cognitive performance include: increased oxidative stress; impaired cellular energy metabolism; perturbed cellular calcium signaling; and the abnormal accumulation of damaged proteins and organelles[8]. Superoxide anion radical, hydroxyl radical, nitric oxide and peroxynitrite are major oxygen free radicals that have been implicated in normal brain aging and cognitive impairment[9]. Protein oxidation and modification by lipid peroxidation products and peroxynitrite increases progressively during aging, and is particularly prominent in the neurons that degenerate in Alzheimer's disease (AD). Likewise, normal aging was associated with increased immunoreactivity for indices of oxidative stress in humans[10], and pathological aging further exacerbated this effect[11]. Oxidative damage to membrane lipids occurs more severely in aged, cognitively impaired animals[12], and to an even greater extent in experimental models of neurodegenerative diseases[13–14]. For example, membrane-associated oxidative stress results in neuronal dysfunction and degeneration by a mechanism involving the lipid peroxidation product 4-hydroxynonenal which covalently modifies proteins critical for cellular ion homeostasis including ion (Na^+ and Ca^{2+}) motive ATPases, and glucose and glutamate transport proteins[15]. Such aberrant oxidative damage likely contributes to an excitatory imbalance that may presage the onset of age-related cognitive impairment and AD[16].

With advancing age neurons may suffer from reduced production of the molecular energy couriers ATP and NAD^+, with impaired mitochondrial function being a principle reason for such a cellular energy deficit[17]. Changes that lead to cellular energy deficits include oxidative damage to mitochondrial DNA and electron transport chain proteins[18], and the plasma membrane redox system[19]. Disease-specific factors may also compromise energy metabolism including Aβ in AD, α-synuclein in Parkinson's disease (PD), huntingtin in Huntington's disease (HD) and Cu/Zn-SOD in amyotrophic lateral sclerosis (ALS)[17]. Aging is also accompanied by accumulation of damaged proteins, nucleic acids and organelles[20–21]. Deficits in proteasomal degradation and molecular repair processes are increasingly recognized as central to age-related CNS dysfunction, particularly following physiological challenges to homeostasis[22–23]. As with oxidative stress, cellular energy deficits and accumulation of damaged molecules and organelles tips the balance of activity in neuronal circuits towards uncontrolled excitation[24].

Dietary energy intake has a major impact on brain aging

Studies of human subjects and animal models support a bidirectional relationship between energy intake and brain function; excessive intake impairs function, while dietary energy restriction enhances function[25]. The underlying mechanisms for this relationship converge on changes in synaptic plasticity and neurogenesis. Diabetes and obesity are common consequences of excessive energy intake that accelerate brain aging by compromising hippocampal neurogenesis and long-term potentiation (LTP), a candidate cellular model for the synaptic changes underlying learning and memory[26]. Excessive caloric intake also increases the risk for neurodegenerative diseases and stroke, possibly by compromising the integrity of the blood-brain barrier[27] resulting in deficient neurovascular coupling. Through these mechanisms and others, conditions arising from excessive energy intake have an impact on brain regions implicated in various facets of cognition.

Perturbation of the levels and rhythmicity of a number of hormones in the context of obesity and the **metabolic syndrome** (Box 1) leads to maladaptive alterations in circuit function that are not restricted to regions traditionally associated with feeding and metabolism. Ghrelin, a hormone produced in the stomach, is one example of a metabolically-relevant peptide that influences cognition and neuroplasticity. Ghrelin acts on the hypothalamic arcuate nucleus to stimulate feeding and promote deposition of adipose tissue[28]. Ghrelin administration enhances hippocampal synaptic density, while loss-of-function results in decreased synapse numbers and impaired Schaffer collateral LTP[29]. Synaptic compromise is associated with behavioral deficits in learning and memory following targeted disruption of the ghrelin gene[29]. In addition to regulating synaptic density, LTP and learning, ghrelin also promotes adult neurogenesis in rats[30]. These findings support a role for ghrelin in hippocampal plasticity, and open the possibility that disruption of ghrelin signaling in the context of obesity could lead to impairment of hippocampal function.

Because pre-existing societal prejudice against obese individuals, studies on the mechanisms related to cognition in obesity should be interpreted cautiously. The perception of obesity as a condition arising from lack of discipline, rather than a disease that, like certain psychiatric conditions, arises from a mixture of environmental pressures and genetic predisposition, often facilitates negative bias among the general public, and could potentially impact opinions among the scientific and communities. It is also important to recognize that experimental observations in genetically homogeneous rodent populations may not always translate to humans. Given these precautions, it should be noted that, for both humans and nonhuman animal models, there is evidence for and against cognitive dysfunction in the context of obesity (Table 1).

The results of human studies reveal a critical window in which obesity, and the metabolic syndrome more generally, has the potential to impact cognitive aging. Exposure to the direct oxidative and indirect endocrine consequences of excessive energy intake during the fourth and fifth decade of life increases the likelihood of cognitive decline during later years[31], while higher body mass indices may not cause cognitive impairment later in life[32]. One interpretation is that the middle-aged brain is most susceptible to the endocrine adversities of the metabolic syndrome, while another hypothesis would suggest that other factors, such as

socioeconomic status, that are correlated with the prevalence of obesity, exert their effects on cognition during this same window. Because some, but not all studies examining cognitive changes in relationship to obesity control for external variables such as socioeconomic status and level of education, the degree to which obesity has an impact on cognition remains an open question.

Research in animal models demonstrates more consistent impairments on various measures associated with learning and memory in rodents exposed to excessive caloric intake. Diets high in fats and simple sugars impair spatial learning in the water maze[33–34], spatial recognition in the Y-maze[35], complex maze learning[36], and operant discrimination[37–38]. However, the time course for memory impairment in rats fed western diets varies. Some studies report memory impairment after two to three months of diet exposure[33, 35, 37], using diets that range from 20% fat to 45% fat; by contrast, another study did not detect cognitive impairment using a diet that was 45% fat until after eight months of diet exposure[34]. Other researchers have failed to detect any impairment at all using diets comparably enriched with fats and simple sugars in mice[39]. Understanding the time course, and underlying cellular and molecular mechanisms, of memory impairment caused by diets that elicit features of the metabolic syndrome is critical in light of evidence for a critical window in humans; however, the question of when, and how, cognitive impairment develops in the context of the metabolic syndrome remains unanswered.

Dietary energy restriction can protect the brain against aging. Early studies showed that lifelong energy restriction through an alternate day fasting regimen improves learning in a complex maze[40]. Caloric restriction also improves memory and Schaffer collateral LTP in young mice[41], and enhances neurogenesis through a brain-derived neurotrophic factor (BDNF)-dependent mechanism[42]. Dietary moderation is also positively associated with successful aging in human populations[25]. Interestingly, age-related impairments in cellular energy metabolism can be reversed by dietary energy restriction[19], as can pathological deficits in learning and memory in AD model mice[43–44]. Dietary energy restriction was also effective in protecting dopaminergic neurons and improving motor function in mouse[45] and monkey[46] models of PD, and protected striatal and cortical neurons and extended survival in a mouse model of HD[47]. A major mechanism by which energy restriction protects neurons against aging and disease is by engaging adaptive cellular stress response pathways that result in the production of a range of cytoprotective proteins including neurotrophic factors, protein chaperones, DNA repair enzymes and mitochondrial uncoupling proteins, among others[48–50] (Figure 2).

Specific dietary components may influence brain aging

Epidemiological data from human populations and mechanistic data from animal models support a protective role for certain dietary phytochemicals[51] and a deleterious effect of saturated fats and refined sugars[52]. Specific macro- and micro-nutrients counteract brain aging by protecting against impairment and promoting adaptive plasticity, or by acting in a permissive or instructive fashion for deficits in neuronal function. For example, regular consumption of refined sugars and saturated fats accelerates age-related deficits in spatial learning[34], whereas consuming relatively high amounts of vegetables and fruits may

counteract the aging process[53]. Emerging evidence suggests that some neuroprotective phytochemicals engage adaptive cellular stress response pathways in neurons to upregulate the expression of neurotrophic factors, antioxidant enzymes, and proteins involved in cellular energy metabolism[51]. In this regard, the biological framework for nutritional neuroprotection conforms to the theory of **hormesis** (Box 2). Phytochemicals that have been shown to protect neurons against dysfunction and degeneration in animal models of neurodegenerative disorders include folic acid[54], thiamine[55], curcumin[56], epigallocatechin-3-gallate[57], plumbagin[58], and resveratrol[59]. Signaling pathways activated by these phytochemicals include the Nrf2 – antioxidant response element (ARE) pathway, the Ca^{2+} - cyclic AMP response element-binding protein (CREB) pathway, and the sirtuin – FOXO pathway (Figure 2). Neuroprotective genes induced by the latter pathways include those encoding neurotrophic factors (e.g., BDNF), protein chaperones (e.g., heat shock protein-70 and glucose-regulated protein-78), antioxidant enzymes (e.g., manganese superoxide dismutase, heme oxygenase-1 and NADH quinone oxidoreductase 1), energy-regulating proteins (e.g., mitochondrial uncoupling proteins), and DNA repair proteins (e.g., AP endonuclease 1). Based on these natural products, medicinal chemists may be able to develop therapeutic agents with greater specificity for a stress response pathway and reduced toxicity.

Physical and cognitive exercise

Evidence in favor of experiential neuroprotection is compelling, and emerging data suggest that lifestyle factors can be harnessed to prevent or treat neurological disease. Physical and mental activities can protect neurons against age-related dysfunction and disease, through a variety of mechanisms including up-regulation of neurotrophic factors, enhanced synaptic plasticity and stimulation of neurogenesis. Lifestyle factors such as cognitive stimulation[60] and aerobic exercise[61] engage a variety of signaling cascades to maintain transcriptional profiles that are more commonly observed in the structurally dynamic developing brain. Such lifestyle factors could, in principle, enhance the efficacy of pharmacological treatments designed to forestall neurodegenerative diseases.

One example of a synergistic interaction between exercise and pharmacological neuroprotection involves the neurotransmitter noradrenaline (Figure 3). Noradrenergic innervation of the hippocampus is necessary for exercise-induced upregulation of BDNF expression[62]. The locus coeruleus (LC) is the origin of noradrenergic fibers, and depletion of LC noradrenaline exacerbates amyloid plaque deposition and cognitive impairment in AD model mice[63]. Both of these studies used loss-of-function pharmacological approaches, but it remains to be seen whether synergistic gain-of-function could be detected through concomitant treatment of AD model mice with exercise and selective noradrenaline reuptake inhibitors (SNRIs; Figure 3).

While healthy aging is accompanied by increased variability in cognitive performance [5–7], aged rats are uniformly more susceptible to memory deficits following an immune challenge[64] (Barrientos et al., 2011). Increased vulnerability to infection-induced learning deficits is accompanied by exacerbation of hippocampal inflammatory responses. Although aged rats run far less than their younger counterparts, even a limited amount of voluntary

wheel running was sufficient to prevent both impaired learning following *E. coli* infection, and attenuate neuroinflammation in the hippocampus[64]. While this study demonstrates that exercise is indeed neuroprotective, no studies to date have addressed whether late-onset physical activity can ameliorate cognitive deficits in a naturally occurring model of age-related cognitive impairment, such as the aged-impaired rat model[5]. Possible interactions between exercise and aging of the noradrenergic system in healthy individuals also remains an open question.

Late-life resilience: it's never too late to make new connections

During the past few decades there has been increased interest in regenerative medicine, largely as the result of major advances in research on stem cells and neurotrophic factors. Here we briefly describe the mechanisms that regulate neurogenesis, and advances in the development of therapeutic interventions that either stimulate endogenous neural stem cells, or involve transplantation of neural progenitors derived from stem cells in embryos or autologous induced pluripotent stem (iPS) cells. Several environmental factors and chemical agents have been shown to stimulate neurogenesis in one or both of the two major populations of neural progenitors in the adult brain, which are located in the hippocampal dentate gyrus and the subventricular zone. Exercise, dietary energy restriction and enriched environments enhance neurogenesis by a mechanism involving upregulation of BDNF expression[65]. The ability of these lifestyle-related factors to enhance neurogenesis is retained during aging, although their efficacy may be attenuated. On the other hand, chronic adverse stressors (e.g., psychosocial stress, depression) and metabolic derangements (e.g., diabetes and insulin resistance) impair neurogenesis by elevating glucocorticoid levels and reducing BDNF expression[66–68]. Unfortunately, because there may not be neural progenitors capable of supplying new neurons to the vast majority of neuronal circuits in the brain, it is unlikely that stimulating endogenous progenitors will be sufficient to repair all damaged circuits in neurodegenerative disorders.

Neuronal replacement by transplantation of neural progenitors, embryonic stem cells or autologous iPS cells is being pursued in preclinical and translational research projects. Numerous studies have documented restorative effects of transplanted stem or progenitor cells in animal models of brain injury or neurodegenerative disorders[69]. Human studies in which human fetal neural progenitors have been transplanted into PD patients have yielded mixed results[70]. Nevertheless, emerging findings with iPS cells generated from fibroblasts or other cell types suggest that transplantation of these cells has beneficial effects in a rodent model of PD[71]. Some of the hurdles encountered in transplantation studies (immune rejection, insufficient trophic support, an 'unfriendly' cellular niche, etc.) might be circumvented by inducing endogenous glial cells to become multipotent neural progenitors which could then be coaxed towards neuronal phenotypes using one or more of the environmental factors described above, or by co-treatment with a neurotrophic factor (see below). For example, glial cells could be infected with an innocuous virus expressing two or three genes that encode proteins that change their cellular phenotype to that of iPS cells or neurons.

Neurotrophic factor replacement via infusion or gene therapy is another promising approach for halting and reversing age-related CNS dysfunction[72]. A long and rich history of preclinical research in animal models, together with considerable clinical experience in AD and PD, suggests that neurotrophic factor-based therapies are likely to counteract disease processes in patients. However, to be successful it is likely that the treatment must be initiated early in the disease process. In addition, such neurotrophic factor therapy assumes that neurons will be responsive (i.e., express functional neurotrophic factor receptors) which in some cases (e.g., insulin-like growth factor/insulin receptors) may not be so[73]. Because neurotrophic factors may not readily cross the blood-brain barrier, there are efforts to develop low molecular weight agonists of neurotrophic factors with high specificity and potency[74], although the potential for adverse effects of such agents on peripheral neurons may hinder their development.

Adherence to lifestyle-based neuroprotection in a deleterious societal milieu

A major implication of the research described above is that successful brain aging is possible for most individuals if they maintain healthy diets and lifestyles throughout their adult life. Unfortunately, this is currently one of the major conundrums in modern societies where high energy food is readily available, exercise is unnecessary in daily routines, and preventative medicine is being suppressed by the actions of the food and pharmaceutical industries. Healthy lifestyle choices should be implemented and incentivized through the coordinated efforts of government, medical schools and health care providers. Moreover, additional research into the mechanisms underlying nutritional and experiential neuroprotection is warranted in order to understand mechanisms which can then be harnessed via pharmacomimetic strategies. Greater awareness of the extent to which physiological aging conforms to a hormetic framework will aid in this effort.

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Box 1: Metabolic syndrome

The metabolic syndrome is a constellation of risk factors that increase the probability of developing diabetes, stroke and cardiovascular diseases. Individuals with the metabolic syndrome have: a high waist-to-hip ratio indicative of central adiposity; elevated fasting glucose levels that, while they may not meet the criteria for type 2 diabetes, indicate that insulin sensitivity may be compromised; elevated triglycerides; and increased blood pressure. The most effective treatment for the metabolic syndrome is weight loss. The endocrine consequences of the metabolic syndrome are not restricted to insulin signaling, but also involve perturbation of leptin levels and sensitivity, changes in corticosteroid synthesis and rhythmicity, and alterations in ghrelin secretion. Because these endocrine factors have each been shown to influence neuronal function[26, 75–76], particularly in the hippocampus, it is likely that the metabolic syndrome could accelerate age-related cognitive deficits. Indeed, recent studies in animal models and human subjects have demonstrated improvements in cognitive performance in response to interventions that increase insulin sensitivity including dietary energy restriction, exercise and pharmacological agents such as glucagon-like peptide 1 analogs[77–80].

Box 2: Adaptive cellular stress response pathways promote successful brain aging through hormesis

Intermittent exposure to mild cognitive or physiological stress increases neuronal resistance to the degenerative disorders of aging[48]. Hormesis – the process through which exposure to low levels of a stressor activates biological repair mechanisms[81] - occurs during exercise, in response to dietary energy restriction and when neurons are stimulated with certain phytochemicals. Hormetic stress stimulates signaling pathways that enhance the abilities of neurons to resist oxidative stress, DNA damage, mitochondrial impairment, and protein misfolding and aggregation. Some of the major proteins involved in such adaptive stress responses include neurotrophic factors, protein chaperones, and proteins involved in mitochondrial biogenesis, protein degradation and autophagy (Figure 2). The cellular signal pathways that mediate hermetic responses in neurons are being identified. For example, cognitive stimulation and exercise involve the activation of glutamate receptors resulting in Ca^{2+} influx, Ca^{2+}/calmodulin-dependent kinases, the transcription factor CREB (cyclic AMP response element binding protein) and induction of genes encoding BDNF and the DNA repair enzyme APE1, among others[60–61]. Dietary energy restriction has been reported to activate genes encoding proteins involved in synaptic plasticity, cellular energy metabolism and cell survival[82]. It has been proposed that there is an evolutionarily conserved network of genes that orchestrate hormetic responses of cells and organisms to various stressful challenges. These so-called ‘vitagenes’ encode proteins critical for the control of protein quality, redox balance, ion homeostasis, membrane integrity and energy metabolism[83]. Examples of phytochemicals that act via hormesis are: sulforaphane (present in relatively high amounts in broccoli) and plumbagin which activate the Nrf2 – antioxidant response element (ARE) pathway resulting in the expression of the antioxidant enzymes HO-1 and NQO1[84]; curcumin (curry spice) stimulates adult hippocampal neurogenesis by inducing a mild cellular stress response involving the extracellular signal-regulated kinases (ERKs)[85]; flavonoids from fruits such as grapes and blueberries enhance learning and memory, possibly by activating sirtuins and CREB[86]. A better understanding of the mechanisms by which phytochemicals stimulate/stress neurons in ways that enhance CNS function and resilience may lead to novel interventions for neurodegenerative disorders.

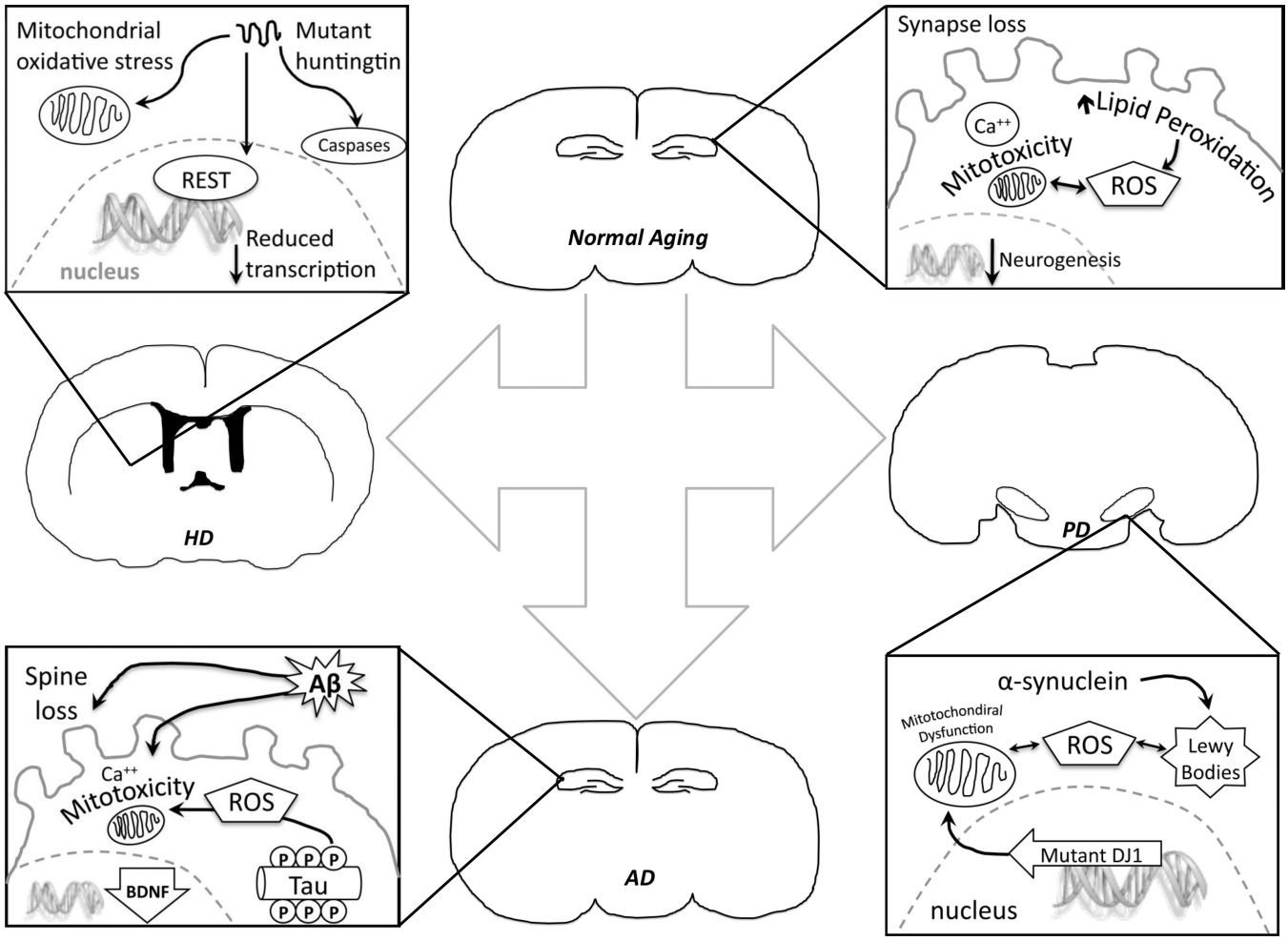

Figure 1. Intrinsic features of normal and pathological aging

Normal aging is accompanied by alterations in neuronal calcium handling and changes in lipid peroxidation, leading to increased generation of reactive oxygen species and damage to mitochondria. These changes are permissive or instructive for the suppression of adult neurogenesis beginning in middle age. Successful aging is characterized by implementation of alternative plasticity mechanisms to compensate for changes in the local microenvironment. Age-related pathologies such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) arise from a combination of genetic and environmental factors, but each disease shares a common feature in that age is a risk factor for disease onset. In this respect, aging sets the stage for the onset of pathology. REST, repressor element 1-silencing transcription factor; ROS, reactive oxygen species, P, phosphorylation site; Aβ, amyloid β-peptide; Ca, calcium; BDNF, brain-derived neurotrophic factor; DJ1, Parkinson protein 7.

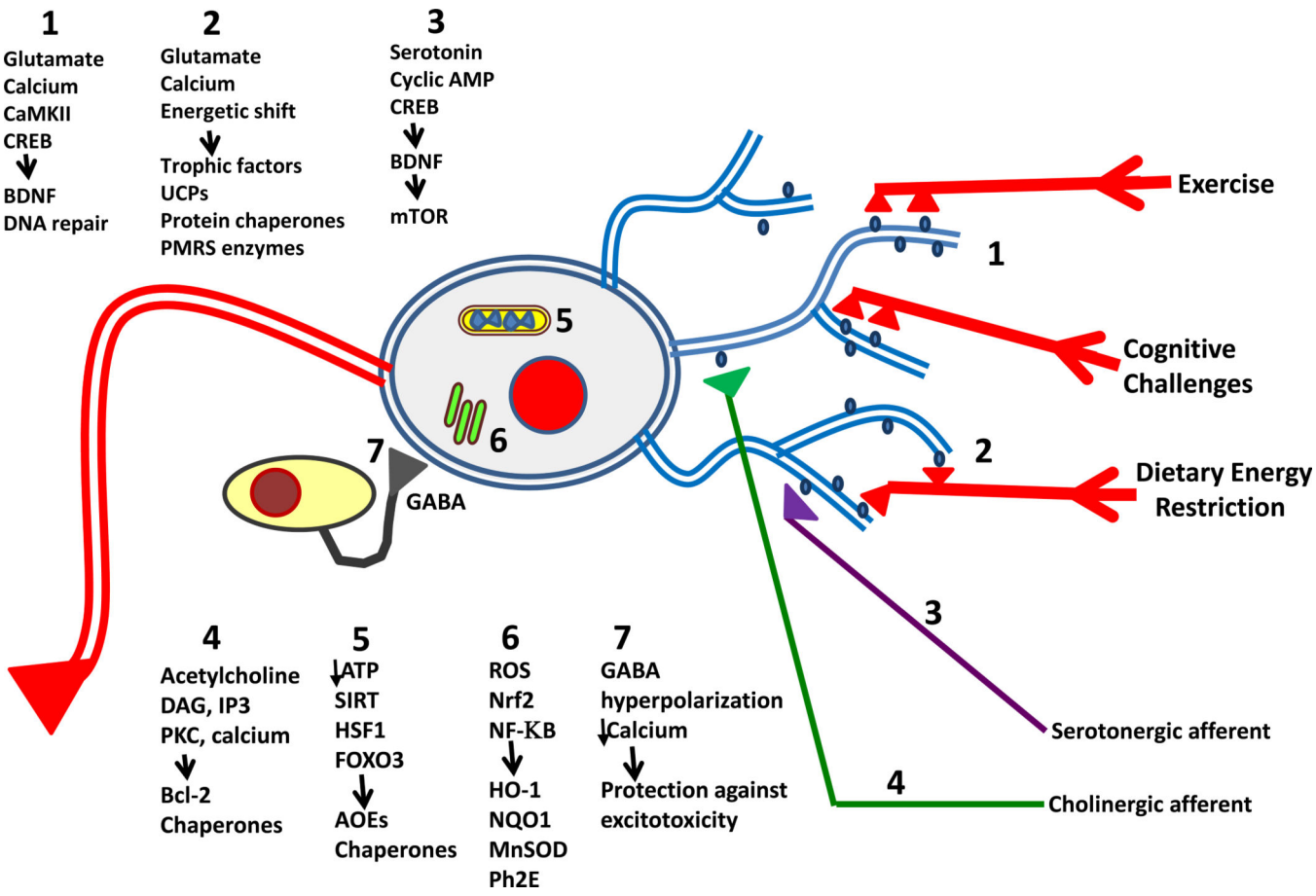

Figure 2. Adaptive cellular stress response signaling mediates beneficial effects of environmental challenges on neuroplasticity and vulnerability to degeneration

A typical glutamatergic neuron in the hippocampus is depicted receiving excitatory inputs (red) from neurons activated in response to exercise, cognitive challenges and dietary energy restriction. In the cell body of the postsynaptic neuron are depicted a mitochondrion (top), the endoplasmic reticulum (left) and the nucleus (right). Examples of seven different adaptive stress response signaling pathways that protect neurons against degeneration and promote synaptic plasticity are shown. During exercise and cognitive challenges postsynaptic receptors for glutamate (1, 2), serotonin (3) and acetylcholine (4) are activated to engage intracellular signaling cascades and transcription factors that induce the expression of neuroprotective proteins including BDNF, mitochondrial uncoupling proteins (UCPs) and anti-apoptotic proteins (e.g., Bcl2). BDNF promotes neuronal growth, in part, by activating mTOR. Mild cellular stress resulting from reduced energy substrates (5) and reactive oxygen species (ROS) (6) engage adaptive stress response pathways including those that up-regulate antioxidant enzymes (AOE) and protein chaperones. Release of γ-aminobutyric acid (GABA) from interneurons (7), in response to activity in excitatory circuits (as occurs during exercise and cognitive challenges), hyperpolarizes the excitatory neurons which can protect them from Ca^{2+} overload and excitotoxicity. BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP response element-binding protein; DAG, diacylglycerol; HO1, heme oxygenase 1; HSF1, heat shock factor 1; MnSOD, manganese

superoxide dismutase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor κB; NQO1, NADH-quinone oxidoreductase 1; Nrf2, nuclear regulatory factor 2; Ph2E, phase 2 enzyme; PKC, protein kinase C; PMRS, plasma membrane redox system; SIRT, sirtuin.

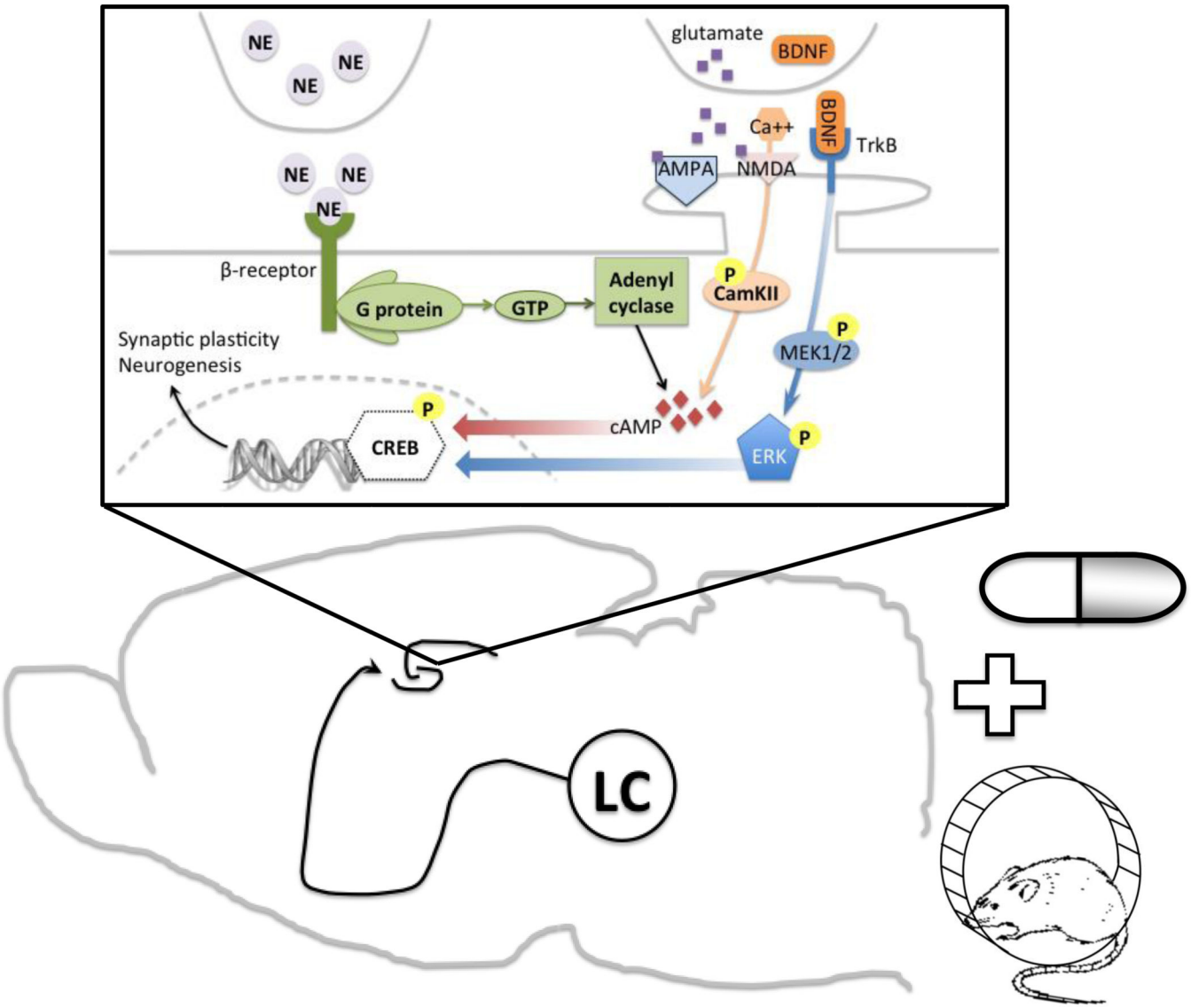

Figure 3. Potential for mechanistic synergy between exercise and pharmacological treatments designed to maintain cognition in an aging population

The locus coeruleus (LC) projection to the hippocampus is essential for exercise-induced brain-derived neurotrophic factor (BDNF) expression. Exercise enhances hippocampal BDNF synthesis, leading to activation of the extracellular signal-related kinase (ERK) pathway, which converges on the transcription factor cyclic adenosine monophosphate (cAMP) response element binding protein (CREB). Treatment with drugs that block norepinephrine (NE) reuptake enhance noradrenergic neurotransmission, leading to activation of adenyl cyclase and cAMP, which also activates CREB, leading to transcription of a number of different genes associated with synaptic plasticity and neurogenesis. Concurrent exercise and norepinephrine reuptake inhibitor treatment could additively enhance hippocampal BDNF production and be neuroprotective. AMPA, {alpha}-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; TrkB, high-

affinity BDNF receptor; CamKII, calcium calmodulin kinase II; MEK1/2, mitogen-activated protein kinase kinase 2; ERK, extracellular-signal related kinase; P, phosphorylation site.

Table 1

Recent studies of cognitive function in relationship to obesity.

Human Studies	Age group	Cognitive outcome
Roriz-Cruz et al. (2007)[87]	Aged	↓
Gunstad et al. (2007)[88]	Adult	↓
van den Berg et al. (2007)[89]	Aged	↑
Sturman et al. (2008)[90]	Aged	—
Li et al. (2008)[91]	Young	↓
Huizinga et al (2008)[92]	Adult	↓
Sabia et al., (2009)[93]	Adult	↓
Volkow et al., (2009)[94]	Adult	↓
Fergenbaum et al. (2009)[95]	Adult	↓
Animal models		
Morrison et al. (2010)[36]	Aged	↓
McNay et al. (2010)[35]	Adult	↓
Granholm et al. (2008)[96]	Adult	↓
Kanoski et al. (2007)[38]	Adult	↓
Mielke et al. (2006)[39]	Aged	—