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Perturbed Energy Metabolism and Neuronal Circuit Dysfunction in Cognitive Impairment

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Summary

Epidemiological, neuropathological and functional neuroimaging evidence implicates global and regional derangements in brain metabolism and energetics in the pathogenesis of cognitive impairment. Nerve cell microcircuits are modified adaptively by excitatory and inhibitory synaptic activity and neurotrophic factors. Aging and Alzheimer's disease (AD) cause perturbations in cellular energy metabolism, level of excitation/inhibition and neurotrophic factor release that overwhelm compensatory mechanisms and result in neuronal microcircuit and brain network dysfunction. A prolonged positive energy balance impairs the ability of neurons to respond adaptively to oxidative and metabolic stress. Experimental studies in animals demonstrate how derangements related to chronic positive energy balance, such as diabetes, set the stage for accelerated cognitive aging and AD. Therapeutic interventions to allay cognitive dysfunction that target energy metabolism and adaptive stress responses (such as neurotrophin signaling) have shown efficacy in animal models and preliminary studies in humans.

Brain energy metabolism and cognitive impairment

Several converging lines of evidence suggest a critical role for alterations in global and regional brain metabolism and energetics in the pathogenesis of cognitive impairment. Epidemiological evidence has implicated global disorders of metabolism (such as obesity and type II diabetes mellitus) in cognitive aging1 and Alzheimer's disease (AD).2،3 Functional neuroimaging, including functional magnetic resonance imaging (fMRI) and 2-deoxy-2[(18)F]fluoro-D-glucose (FDG) positron emission tomography (PET) studies, have demonstrated regional metabolic changes correlating with cognitive impairment.4،5 Animal studies have established several links between these conditions, demonstrating mitochondrial and metabolic alterations in the brains of cognitively impaired animals6،7،8 and abnormal cognition and neuronal changes 9،10،[11] in the brains of metabolically impaired animals. On the other hand, data suggest that manipulations that improve global energy metabolism (such as caloric restriction and exercise) may be effective in preventing[12،]13 or reversing14،15 cognitive impairment and attenuating the atrophy[16،17] associated with brain aging and AD in humans and animals.[18،19،20]

Search strategy: PubMed articles published between 1990 and the time of writing. Searches included various combinations of the following terms: Alzheimer, cognitive, energy metabolism, network, excitatory, GABA, glutamate, amyloid, mitochondria, neurotrophic factors, diabetes, exercise, oxidative stress.

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A separate line of research implicates brain network dysfunction in cognitive impairment. Our complex cognitive functions and behavior are the emergent property of the brain's hierarchical organization,[21] which is based on nerve cells anatomically and functionally linked to form microcircuits, which in turn interconnect to constitute large-scale brain networks.[22] The brain is organized in such a way that information processing takes place efficiently and economically in terms of metabolic costs.[23] This suggests a fundamental link between brain energetics and network function, which is consistent with the fact that network dysfunction develops in the course of cognitive aging and AD, in parallel with metabolic derangements.

How could brain network dysfunction be linked to global or regional energetic derangements? Recent evidence has reinforced the old idea that neurodegenerative diseases, in particular AD, preferentially target specific networks.[24,25,26] Within brain networks, a small number of nodes, referred to as connector hubs, have disproportionately numerous connections through which they integrate the functions of distant microcircuits.[26] Connector hub nodes are vital for information flow over a whole network; their dysfunction from regional metabolic derangements secondary to neurodegenerative pathology may critically affect a network's function[22] resulting in phenotypic manifestations at the levels of cognition and behavior. Moreover, it has become evident that aging alters the way networks process information and handle cognitive tasks globally,[23] in parallel with global changes in brain metabolism.

In this article, we review research on the relation of the brain's organization in microcircuits and networks to the spread of AD on a background of aging-related changes in energy metabolism. We consider the evidence for adaptive changes in microcircuit and network activation in response to pathologic processes, such as the balance of excitatory/inhibitory synaptic activity and neurotrophic factor production, and show how these adaptations relate to regional neuroenergetics. Finally, we relate these processes to whole-organism energetics and show how a positive energy balance caused by excessive caloric intake and a sedentary lifestyle favors cognitive aging and the AD cascade by impairing adaptive responses.

Selective vulnerability in AD: connectivity and energetics

A body of neuroimaging research has established that manifestations of early AD relate to specific network dysfunction resulting from atrophy27 and hypometabolism within critical nodes.[28] MRI-documented atrophy in early AD is most prominent in medial temporal lobe (MTL), extending over time into inferior temporal, temporal pole, inferior parietal, superior frontal, posterior medial cortex (PMC, consisting of posterior cingulate cortex and precuneus), inferior frontal, and superior parietal regions.[29] Hypometabolism on FDG-PET evolves temporally through a similar regional pattern.30 The early involvement of parietal cortex correlates with decline in processing visuospatial information,31 whereas, the early involvement of MTL and PMC nodes of the episodic memory and default mode networks are responsible for key AD deficits in episodic and semantic memory (Figure 1). It is still unclear what determines this selective regional vulnerability in AD. Nevertheless, mounting evidence suggests that pathologic changes spread into regions that are energetically challenged and receive neuronal projections from regions already exhibiting pathology.

We share the view that a cohesive narrative for the temporal progression of AD cannot be constructed without reference to connectivity and energetics.[26] Connectivity is necessary (although not sufficient) to explain the differential spatial and temporal spread of the two pathological landmarks of AD: extracellular deposits of amyloid β-peptide (Aβ), assuming various plaque formations, and intracellular neurofibrillary tangles, NFTs, consisting of hyperphosphorylated self-aggregating tau.[24,32,33] There are conspicuous anatomical

connections between sequentially affected areas in AD. Aβ deposition occurs at a constant slow rate at various neocortical locations in some older individuals34 (Figure 2). NFTs, on the other hand, appear first at the subiculum and entorhinal cortex (layer II/III and layer IV) accompanied by synaptic and cellular loss.24,32 Cells in layer II and adjacent parts of layer III affected by NFTs are precisely those that receive lateral connections from (transmodal) neocortex, and, in turn, project to the hippocampus proper or cornu ammonis (CA).24,35 Layer III neurons generate the glutamatergic perforant path pathway that terminates on distal dendrites of CA1 neurons, while layer II neurons project to CA3 pyramidal neurons that, in turn, give rise to the Schaffer collateral pathway that terminates on the apical dendrites of CA1 neurons. The loss of enthorhinal neurons deprives the hippocampus of neocortical input35 and directly impairs its function and plasticity.36 On the other hand, the affected cells in layer IV send lateral connections to transmodal neocortex;[24] loss of these cells deprives the PMC and other transmodal cortices from hippocampal input.

Neocortical involvement in AD can be largely attributed to connectivity to MTL allocortex; transmodal areas directly linked to it are the most vulnerable, whereas motor and primary sensory areas that are not directly connected to it are least affected[24] (Figure 1). This selective vulnerability is not attributable to cytoarchitecture: transmodal areas not directly linked to MTL (such as the portion of anterior cingulate cortex, which is linked with motor areas) are spared.[37] Moreover, lack of involvement of a brain region in AD does not imply resistance to neurodegenerative cascades in general, since frontoinsular and anterior cingulate areas are spared in AD but degenerate in behavioral variant Frontotemporal Dementia.38 Supporting the notion that connectivity determines regional vulnerability in AD, a pattern of involvement similar to the cortex is seen in the thalamus: Aβ deposits and NFTs are confined to nuclei with limbic connections.39

What could the mechanisms be for the spread of AD through anatomical connections? Cellular and animal studies have shown that soluble Aβ oligomers accumulate at the synapses40, where they impact a delicate balance of excitation/inhibition41,42, impair long term potentiation[43] and facilitate long-term depression (two types of synaptic plasticity critical for learning and memory).[44,45] Axons and synapses are selectively vulnerable to intracellular accumulation of pathologic substrates and may be the site where the nerve cell death process is triggered.46 Aβ oligomer accumulation in synapses may, therefore, result in tau hyperphosphorylation and aggregation in axons, which may be transferred to the neuronal soma in the form of a NFT, far from the site of Aβ deposition.

While connectivity partly explains the spread of AD, it does not account for the origin of the disease in specific neocortical and MTL areas. Instead, this localization may partly be accounted for by aging and age-related metabolic disease, which render MTL neurons particularly vulnerable to the energetic stress related with AD extracellular and intracellular deposits. Neuroimaging evidence suggests reduced efficiency of energy metabolism and disproportionate metabolic cost for cognitive processing in the hippocampus, parahippocampal gyrus and amygdala (as well as PMC, frontal and temporal transmodal nodes).23 Animal studies have shown that hippocampal pyramidal neurons have the highest energy requirements of any neurons in the brain47 and may therefore be at risk under conditions of unmet metabolic needs. Aging-related cognitive impairment in rats is associated with down-regulation of insulin signaling and glucose utilization pathways.48 In hippocampal pyramidal neurons, aging and chronic hyperinsulinemia synergistically up-regulate the gene for the glucocorticoid receptor (GR) and genes for inflammatory/immune pathways and down-regulate insulin signaling genes, thereby blocking glucose utilization and decreasing mitochondrial function.6 The end-result of chronic hyperinsulinemia is MTL atrophy.49

Turning our attention to affected neocortical areas, the PMC and medial prefrontal hubs of the default mode network show early functional impairment in AD,[5,50] associated with Aβ deposition.[51,52] We view this vulnerability as the result of their recruitment to compensate for failing hippocampal function with aging and in the early stages of AD. Successful memory encoding depends on the dynamic balance of hippocampal activation and PMC deactivation.53 PMC deactivation decreases with age-related cognitive impairment53 and successful memory encoding can only be maintained by hippocampus hyperactivation. Similarly, in aging and early AD, greater activation of the hippocampus, PMC and frontal areas is required for successful memory retrieval.54,55 This increased hippocampal recruitment presumably translates into a chronic increase of the energy requirements of its neurons. With AD progression (clinically at the stage of late MCI), PMC deactivation during encoding is attenuated further,[56], especially among APOE ε4 carriers, suggesting that it represents an aspect of AD pathophysiology. Given that unrestrained episodic retrieval and semantic processing occupy brain activity whenever the brain is not engaged in specific cognitive tasks [representing the "default" functional state of the brain], this lack of deactivation translates into a chronic increase in the energy requirements of default network nodes. Eventually, atrophy due to neuronal death occurs in affected default mode network nodes resulting in severe hypometabolism.28

Excitatory and inhibitory signaling dysregulation in aging and AD

Given that much of the energy consumed by neurons is used for synaptic signaling,[57] neuronal energetics are intricately linked to neurotransmission. The vast majority of the brain's neurons and synapses deploy either the excitatory neurotransmitter glutamate or the inhibitory neurotransmitter GABA, while other neurotransmitters (serotonin, norepinephrine, dopamine and acetylcholine) and neuropeptides (somatostatin, corticotrophin-releasing hormone, neurokinins, etc.) fine tune the activity in neural networks.[58] Nerve cell microcircuits within different brain regions are organized in a fundamentally similar fashion (Figure 3). Glutamate released from presynaptic terminals activates AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionate) receptors resulting in depolarization of the postsynaptic membrane and Ca^{2+} influx through NMDA (N-methyl-D-aspartate) receptor channels and voltage-dependent Ca^{2+} channels (Figure 4). Ca^{2+} serves as a second messenger that activates cascades of enzymes (protein kinases, nitric oxide synthase and proteases) and transcription factors (CREB, AP1 and others) that mediate rapid or delayed biochemical and structural changes, and may also increase the resistance of the neurons to disease. Perturbations in the balance between glutamatergic and GABAergic signaling occur early in the development of age-related cognitive impairment and AD, resulting from and contributing to disturbed cellular metabolism. Moreover, normal synaptic activity reduces Aβ production and protects synapses against Aβ-related alteration.[59]

An inhibitory imbalance (induced by GABA receptor agonists or glutamate receptor antagonists) impairs synaptic plasticity and associated learning and memory processes in animals and human subjects.[60] Conversely, excitatory imbalance resulting from excessive glutamate receptor activation and/or reduced GABAergic signaling can result in seizures and degeneration of synapses and neurons.61 Complex microcircuit alterations affecting regional excitatory/inhibitory balance do occur in aging and AD in the hippocampus and cortex. Studies in animals have demonstrated that aging decreases GABAergic signaling in the hippocampus,62 resulting in excitatory imbalance, while at the same time aging impairs neuronal glucose uptake, causes mitochondrial dysfunction, and activates glucocorticoid pathways6 rendering neurons vulnerable to glutamate-induced damage.[63] The excitatory imbalance of aging may be exacerbated by AD, since Aβ promotes membrane depolarization and renders human cortical neurons vulnerable to glutamate-mediated Ca^{2+}

overload in vitro,[64] which may lead to emergence of hyperactive neuronal clusters in the vicinity of plaques, as has been demonstrated in a rat model of AD.[42] The emergence of such clusters may account for the increased metabolism in nodes of the default mode network associated with high regional PIB binding, which is seen transiently in the AD before atrophy prevails.[28] The excitatory imbalance in AD may also result in increased occurrence of epilepsy in AD patients.[65] Paradoxically, AD may also cause a regional inhibitory imbalance: hippocampal synaptic plasticity is impaired in AD mice due to reduced NMDA receptor activity,[66] whereas Aβ can reduce seizure-like activity in cultured hippocampal neurons induced by GABA receptor antagonists.[67] To reconcile these facts, we should note that, in mouse models of AD, there is initially increased hippocampal and cortical excitability followed by GABAergic sprouting, increased inhibitory transmission and impaired synaptic plasticity.[41]

The expression of genes encoding proteins involved in the regulation of neuronal excitability is altered in brain aging and AD. Age-related modifications of gene promoter regions are associated with reduced expression of genes encoding proteins involved in synaptic plasticity (e.g., glutamate and GABA receptor subunits, synaptic vesicle proteins) and cellular Ca^{2+} homeostasis (Ca^{2+} binding proteins, Ca^{2+} dependent kinases and Ca^{2+} transporters) in humans.[68] Alterations in the expression of genes involved in synaptic plasticity and Ca^{2+} metabolism regulation have been documented in animal models of aging and AD and older humans.[69,70] The down-regulation of inhibitory signaling and Ca^{2+} binding proteins may render the neurons vulnerable to Ca^{2+} overload. Our group has recently demonstrated that chronic experimental silencing of cortical neurons in vitro results in molecular changes similar to those seen in aging and AD, including reduced expression of genes involved in GABAergic transmission, inhibitory neuropeptides, calcium buffering, and calmodulin- and CREB-mediated signaling.[71]

The events downstream of perturbed network activity and dysregulated cellular energy metabolism that lead to neuronal death may also include accumulation of DNA damage and impaired removal of damaged proteins and organelles. For example, the expression of genes involved in DNA repair and removal of damaged proteins are suppressed in multiple regions in the mouse brain during aging.[72] Physiological levels of glutamate receptor activation up-regulates DNA repair gene expression[73] and induces the movement of proteasomes from dendritic shafts into synaptic spines[74] in cultured rat neurons, protecting themagainst the accumulation of damaged DNA and proteins. Nerve cell microcircuit perturbations in AD may impair these important housekeeping processes.

The survival and growth of neurons is supported by neurotrophic factors produced by neurons or glial cells. Brain-derived neurotrophic factor (BDNF) is produced by neurons throughout the brain, where it is released in an activity-dependent manner (Figure 5A). BDNF plays pivotal roles in synaptic plasticity, learning and memory and neurogenesis, and can protect neurons against metabolic and oxidative insults.[46] In addition, BDNF enhances intracellular energy availability to cultured mouse neurons by increasing expression of glucose transporters and stimulating amino acid transport.[75] Studies of transgenic mouse models of AD indicate that large Aβ oligomers suppress BDNF production,[76] disrupt its ability to activate the transcription factor CREB,[77] and block the retrograde trafficking of BDNF from synaptic terminals to the nucleus impairing its ability to promote neuronal survival.[78] Selective blockade of NMDA receptors mimics the abnormal molecular phenotypes of electrically silenced neurons, and treatment with BDNF reverses the perturbations caused by chronic suppression of neuronal activity. These findings suggest that activity-dependent neurotrophic signaling is impaired in brain aging and AD. Indeed, it was reported that cerebrospinal fluid BDNF declines in humans with aging and even more so in AD patients.[79]

Molecular alterations in AD are associated with perturbed neuronal energy metabolism

The process of Aβ oligomer formation in neuronal rat cultures generates hydrogen peroxide and hydroxyl radical, which then induce lipid peroxidation in the plasma membrane of neurons and glial cells and impair the function of ion-motive (Ca^{2+} and Na^{+}/K^{+}) ATPases and glucose transporters; as a result cellular Ca^{2+} and energy homeostasis are perturbed and synaptic function is impaired (Figure 4).[80] In addition, AD pathogenesis may be linked with excessive accumulation of Ca^{2+} in the endoplasmic reticulum, which contributes to synaptic dysfunction and neuronal degeneration.[81] In vivo imaging of intracellular Ca^{2+} levels in cortical neurons in a mouse model of AD revealed that some neurons are hypoactive, whereas neurons in the vicinity of Aβ plaques are hyperactive.[42] The latter findings are consistent with the excitoxicity/energy depletion hypothesis of neuronal degeneration in AD.[46]

Impairment of mitochondrial function occurs in vulnerable neurons in MCI and AD and likely results from a combination of factors including Aβ oligomer accumulation, oxidative stress and a deficit in neurotrophin signaling.[82] A reduction in the activity of several mitochondrial enzymes (e.g., α-ketoglutarate, pyruvate and isocitrate dehydrogenases) is evident in brain tissue samples from AD patients,[83] and experimental findings in animal models of aging and AD suggest that mitochondrial dysfunction is both necessary and sufficient for impaired cognitive function.7,8 Mitochondria are located in presynaptic terminals and dendrites where they play important roles in local Ca^{2+} signaling and associated processes involved in synaptic plasticity.[82,84] These synapse-associated mitochondria may be particularly vulnerable, and so may be compromised early in the AD process.

Perturbed cellular energy metabolism and associated oxidative stress are also involved in the hyperphosphorylation and self-aggregation of tau. In a mouse model of Down syndrome with a subset of triplicated human chromosome 21 ortholog genes (including amyloid precursor protein, APP), mitochondrial membrane potential and ATP production are reduced in brain cells and tau is hyperphosphorlyated due to an increase in GSK3β and JNK activities.[85] Among the many kinases that can phosphorylate tau, data from AD mouse models strongly implicate GSK3β in the pathogenesis of AD.86 GSK3β may play important roles in Aβ processing87 and in linking perturbed cellular energy metabolism and cognitive decline in aging and AD. Agents that inhibit GSK3β reduce tau hyperphosphorylation, enhance cognitive function and reduce Aβ production in mouse models of AD.88 GSK3β suppression enhances glucose uptake by several cell types[89] and increases brain insulin-like growth factor 1 (IGF-1), which is decreased in AD,[90] in mouse model of AD. These data suggest an important link between AD pathogenesis and brain energy metabolism amenable to pharmacologic interventions.

Impact of energy intake and expenditure on cognitive aging

High-energy diets and diabetes may have adverse effects on cognitive function in aging and AD, whereas dietary energy restriction may have beneficial effects (Figure 5). Here we review experimental data in animals supporting these claims. In rhesus monkeys, aging is associated with decreased number (or activity) of functional mitochondria in the hippocampus and a negative correlation exists between metabolic syndrome severity and oxidative function of these mitochondria.[6] Rodents fed with fats and/or simple sugars exhibit poor learning and memory compared to animals on lower energy diets,9 and even in young animals excessive weight impairs some cognitive domains.10 On the other hand, in a mouse model of accelerated aging, caloric restriction attenuated age-related deficits in

learning and memory.91 Life-long caloric restriction in mice prevents age-related declines in learning,[92] and preserves spatial and non-spatial and working memory in aged rats.[93] Even when initiated in mid-life, dietary energy restriction preserves cognitive functions in aging mice.[94] In mouse models of AD, high-energy diets exacerbate Aβ deposition and memory impairment,[95] whereas dietary energy restriction prevents[96] or attenuates[97] the development of cognitive impairment and Aβ and tau pathologies.

Three general mechanisms by which excessive energy intake adversely affects cognitive function are increased oxidative stress, inflammatory processes and impaired adaptive cellular stress responses. Oxidative damage to proteins and DNA is elevated in brain cells of animals on high-energy diets[98] and reduced in animals on low energy diets.[99] High-energy diets promote inflammatory processes in the brain associated with cognitive impairment.[100] On the other hand, dietary energy restriction protects neurons and synapses in animal models in which neurotoxicity is mediated by oxidative stress.[101] Alternate day fasting reduced brain damage and improved functional outcome in an animal model of stroke by a mechanism involving suppression of brain inflammation. The effectiveness of dietary restriction was reduced in older animals, perhaps as a result of age-related impairment of adaptive cellular stress response pathways.[102]

Particularly interesting is emerging evidence that excessive dietary energy intake impairs,[100] whereas dietary energy restriction increases BDNF signaling.[102] Animal studies in which BDNF or its receptor trkB have been genetically manipulated, or BDNF has been administered to the brain, have demonstrated major roles for BDNF in synaptic plasticity, learning and memory and neuronal resistance to oxidative, metabolic and excitotoxic insults relevant to cognitive dysfunction and AD.[46] BDNF also enhances neurogenesis in the hippocampus, which may contribute to maintenance of hippocampal neurons and preservation of cognitive function during aging.[103] Leptin receptor mutant diabetic mice that have reduced BDNF levels exhibit cognitive impairment and impaired synaptic function and neurogenesis.[11] BDNF signaling also plays major roles in energy metabolism and cognitive function in humans as demonstrated by the cases of human subjects with BDNF haploinsufficiency[104] and with de novo trkB mutations[105] who are obese, insulin resistant and cognitively impaired.

Impaired cellular energy metabolism accompanies increased oxidative stress, as indicated by reduced expression and/or activity of mitochondrial proteins and oxidative genomic damage.[106] The most common metabolic disease, diabetes impairs learning and memory in animals by inducing multiple alterations in hippocampal microcircuits, including reduced dendritic spine density, impaired synaptic plasticity and reduced neurogenesis.[11] Diabetes may impair cognitive function, in part, by hyperactivation of the hypothalamic-pituitary-adrenal axis and lowering glucocorticoid levels can restore cognitive function, synaptic plasticity and neurogenesis.[11] The links between diabetes and AD are complex and likely also involve inflammatory mechanisms: in double-mutant AD transgenic and diabetic mice, the onset of diabetes exacerbates AD-like cognitive dysfunction without an increase in brain Aβ burden, but in association with cerebrovascular inflammation.[107]

Animal studies have demonstrated benefits of exercise on cognitive function during normal aging and in models of insulin resistance/diabetes and AD, and have elucidated the underlying mechanisms (Figure 5). Several studies have documented beneficial effects of exercise in mouse models of AD, such as improved cognitive performance.[18] Exercise reduces glucocorticoid levels and enhances hippocampal neurogenesis.[19] Mild metabolic challenges associated with exercise induce the expression of genes encoding proteins that enhance the ability to resist perturbations and cellular plasticity, therefore enhancing learning. Exercising rats exhibit increased levels of proteins involved in cellular energy

metabolism and synaptic plasticity in the hippocampus.[20] The hippocampal transcriptome of old mice that have been running lifelong exhibit greater learning-induced activation of synaptic plasticity and mitochondrial function genes, and down-regulation of oxidative stress and lipid metabolism genes; running also modulates genes involved in cell excitability, energy metabolism, and insulin signaling.[108] We should take particular notice of the fact that exercise impacts cognition by enhancing learning. This may explain why certain studies have failed to show a beneficial effect of exercise on cognition independent of cognitive stimulation.[109]

In regards to the cellular and molecular mechanisms underlying the cognition-enhancing effects of exercise, BDNF plays a pivotal role. Even short-term exercise may improve memory in rats, associated with increased hippocampal BDNF.[110] Exercise and caloric restriction each increase hippocampal dendritic spine density and BDNF levels in diabetic mice and exercise significantly enhances the effect of caloric restriction on spine density and BDNF levels.[111] Exercise-induced BDNF may strengthen existing synapses, promote synaptogenesis and stimulate neurogenesis.19,46 The effects of exercise may not occur simultaneously across cognitive domains; instead, memory retention appears best immediately after a period of exercise, associated with BDNF elevation, whereas memory acquisition is improved after a post-exercise delay.112 A second crucial mediator of the brain effects of exercise is the peripherally produced IGF-1, which induces plastic and neuroprotective brain changes and stimulates hippocampal neurogenesis.[113] Finally, two proteins that play important roles in cognitive processes, mitogen-activated protein kinase and the transcription factor CREB (cyclic AMP response element-binding protein), are also increased in the hippocampus of rats in response to exercise.[114]

Energy-based therapeutic interventions in cognitive aging and AD

Thus far, most of the funds for basic and translational research on AD have been invested in developing treatments to halt the production of Aβ or enhance its removal, which have, thus far, failed in clinical trials. Here we consider alternative approaches that show promise in preclinical and preliminary clinical studies and aim at prophylaxis and slowing of cognitive decline based on modulating adaptive cellular stress response pathways and energy metabolism.

The considerable evidence that diabetes is a risk factor for cognitive impairment and AD has led to preclinical studies aimed at establishing the efficacy of anti-diabetic treatments in animal models.[93,96,115] At the cellular level, insulin was shown to decrease binding of Aβ oligomers at the synapses and the oxidative stress and synaptic spine deterioration they cause.116 Several small studies have suggested that insulin treatment improves cognitive function in patients with MCI or AD. In one study, subcutaneous insulin-treated patients with coincident AD exhibited significantly less cognitive decline compared to placebo-treated patients.117 In another study, intranasal insulin improved cognitive performance in AD patients.118 Despite the disappointment caused by the negative trial of the insulin-sensitizing agent rosiglitazone in AD,119 modulation of insulin signaling pathways continues to appear as a promising target for AD therapeutics. Particularly promising for the treatment of cognitive impairment and AD, particularly in insulin resistant subjects, are the GLP-1 (glucagon-like peptide 1) receptor agonists. GLP-1 receptors are widely expressed in neurons throughout the brain and data suggest that their activation enhances synaptic plasticity and cognitive performance and promotes neuronal survival.120 Recent preclinical studies have demonstrated beneficial effects of GLP-1 receptor agonists in animal models of AD, including protective and restorative effects on synaptic plasticity and cognitive function.115,121 Similarly, treatment of AD mice with sitagliptin (which inhibits the enzyme that inactivates GLP-1 in the blood, DPP4) resulted in increased brain levels of

GLP-1, ameliorated memory deficits and reduced levels of oxidative stress.122 A protease-resistant analog of GLP-1 called Exendin-4 was developed and is now widely used for treatment of diabetes. Because of its dual actions on glucose metabolism and neurons affected in AD, clinical trials to test the efficacy of Exendin-4 in human subjects with MCI and early AD have recently been initiated.

Given the multiple neuroprotective actions of neurotrophic factors, such as nerve growth factor (NGF) and BDNF, they have great potential as therapeutic agents in AD, as well as against aging-related cognitive decline. Unfortunately, they exert pleiotropic effects and it is difficult to deliver them at the site of pathology. Therefore, small molecules selectively targeting specific neurotrophin receptors show greater promise for modulating neurotrophin signaling via systemic delivery.[123] An alternative approach is gene therapy. Intraparenchymal NGF gene delivery to the basal forebrain of aged rhesus monkeys restored cholinergic neuronal markers to levels of young monkeys,124 whereas NGF gene transfer into the septum of aged rats increased the number of cholinergic neurons and acetylcholine release.125 NGF and recombinant hNGF-61 were successfully delivered via ocular and intranasal administration to transgenic AD mice, in which they suppressed AD pathology.[126,127] In aged rats and non-human primates, local BDNF delivery reverses neuronal atrophy and ameliorates age-related cognitive impairment, whereas in transgenic AD mice, BDNF gene delivery reverses synapse loss, partially normalizes aberrant gene expression, improves cell signaling and restores learning and memory.[128]

Finally, there is a potential for sustaining and restoring functional circuits in the aging brain by providing neurons with chemicals that elevate levels of the energy substrates adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD^+). Best known for its ability to preserve ATP levels in muscle cells thereby enhancing endurance, creatine can also protect neurons against oxidative and metabolic insults, including Aβ toxicity,[129] in vitro or against traumatic brain injury in vivo.[130] Administration of nicotinamide, which increases cellular NAD^+ levels in the brain, improved cognitive function in old rats[131] and in a mouse model of AD.[132] Preliminary human studies suggest that dietary niacin, which consists of nicotinamide and nicotinic acid, can reduce the risk of age-related cognitive decline and AD.[133] Another approach to enhancing neuronal bioenergetics is to target mitochondrial potassium channels; our group has recently demonstrated improvements in cognitive function and reductions in Aβ and tau pathologies in AD mice treated with the mitochondrial potassium channel opener diazoxide [134]. Because creatine, nicotinamide and diazoxide are all approved for use in humans, clinical trials in subjects with MCI and AD could be initiated without delay.

Conclusions

From this review, it is evident that multiple mechanisms that largely depend on the organism's state of energy metabolism adaptively modify neuronal and brain networks. The value of a lifestyle that stimulates the brain's adaptive responses via regular exercise, moderation of dietary energy intake and intellectual vigor cannot, in our view, be overstated. The available evidence suggests that these three brain-healthy habits protect cells against the adversities of aging and AD by engaging cellular stress response pathways that induce the expression of genes encoding proteins involved in cytoprotection and synaptic and neurogenic plasticity (Figure 5A). Approaches that enable such brain-healthy lifestyles should be developed and widely implemented. Novel patterns of food intake should be considered in light of the recent evidence that alternate day caloric restriction diets can be adhered to and improve health dramatically.[135] Finally, from a drug discovery for AD perspective we propose an alternative focus to Aβ metabolism, to the levels of whole body and cellular energy metabolism and stimulation of adaptive cellular stress responses.

Pharmacological approaches should also pursue reasonable targets, such as agents that suppress inflammation or enhance mitochondrial function.[136] Whether these conceptual changes are going to be successful in preventing and treating cognitive aging and AD is an open question and a challenge.

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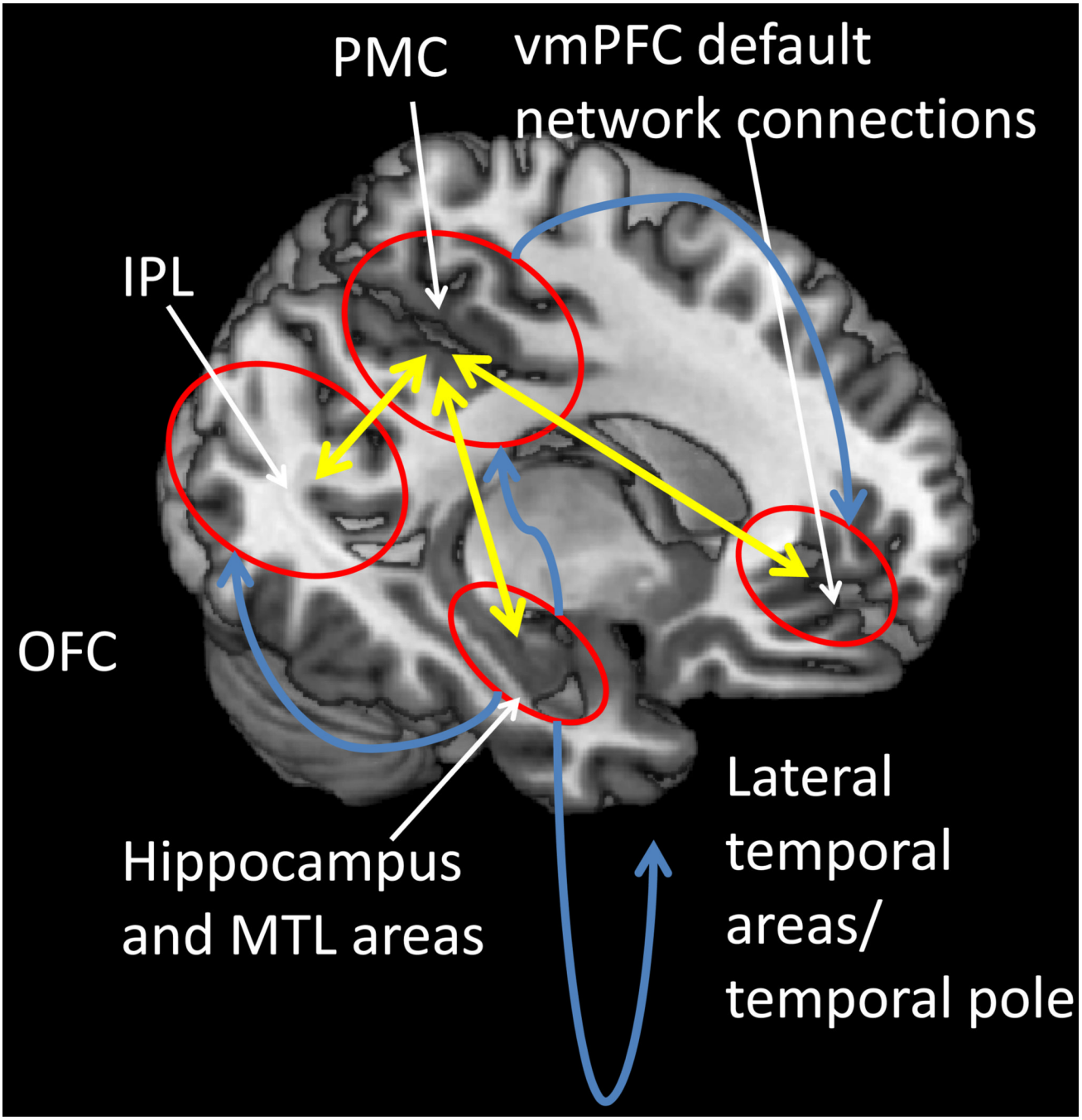


Figure 1.
Spread of the neuropathology in AD. Neurofibrillary tangles and neurodegeneration first appear in entorhinal cortex, and then in other medial temporal lobe (MTL) structures; fibrillary Aβ deposits and plaques first appear in transmodal areas [such as the posterior medial cortex (PMC), the inferior parietal lobule (IPL) and the lateral temporal lobe and temporal pole] that maintain reciprocal connections (illustrated by yellow arrows) with the entorhinal cortex. Spread of neurofibrillary tangles and neurodegeneration (illustrated by blue arrows) does not correlate with the spread of fibrillary Aβ deposition and plaque formation.

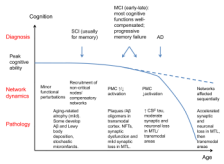


Figure 2.

Evolution of cognitive ability with age, in the presence or absence of AD pathology: schematic progression of pathology, brain network dynamics and clinical manifestations. SCI: subjective cognitive impairment; MCI: mild cognitive impairment; AD: clinical Alzheimer's disease; NFTs: neurofibrillary tangles; PMC: posterior medial cortex; MTL: medial temporal lobe.

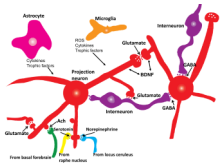


Figure 3.

Basic organization of neuronal microcircuits that control information flow through all brain regions involved in cognitive processing. The major excitatory projection neurons are glutamatergic with long axons that synapse on dendrites of other glutamatergic neurons that may, in turn, project their axons to a different brain region. GABAergic interneurons receive excitatory inputs from glutamatergic neurons and form synapses on the cell bodies of the same or other glutamatergic neurons. Glutamatergic neurons also receive synaptic inputs from noradrenergic, serotonergic and cholinergic neurons whose cell bodies are located in the locus ceruleus, raphe nucleus and basal forebrain, respectively. Neurons in all brain regions also interact with glial cells including astrocytes and microglia which produce trophic factors and cytokines which may normally play important roles in synaptic plasticity. However, excessive production of pro-inflammatory cytokines and reactive oxygen species (ROS) by glial cells has been implicated in the pathogenesis of cognitive impairment and AD.

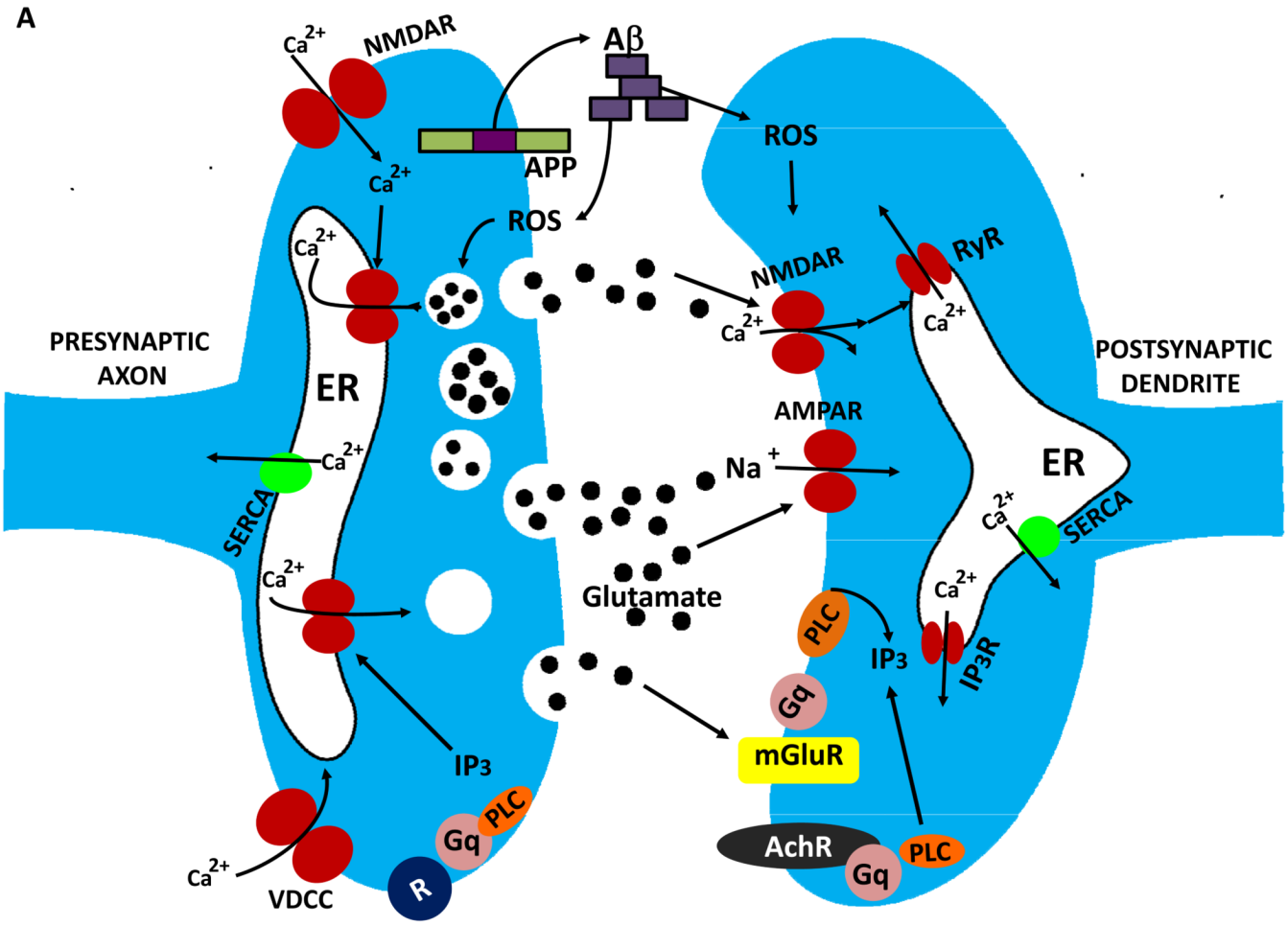
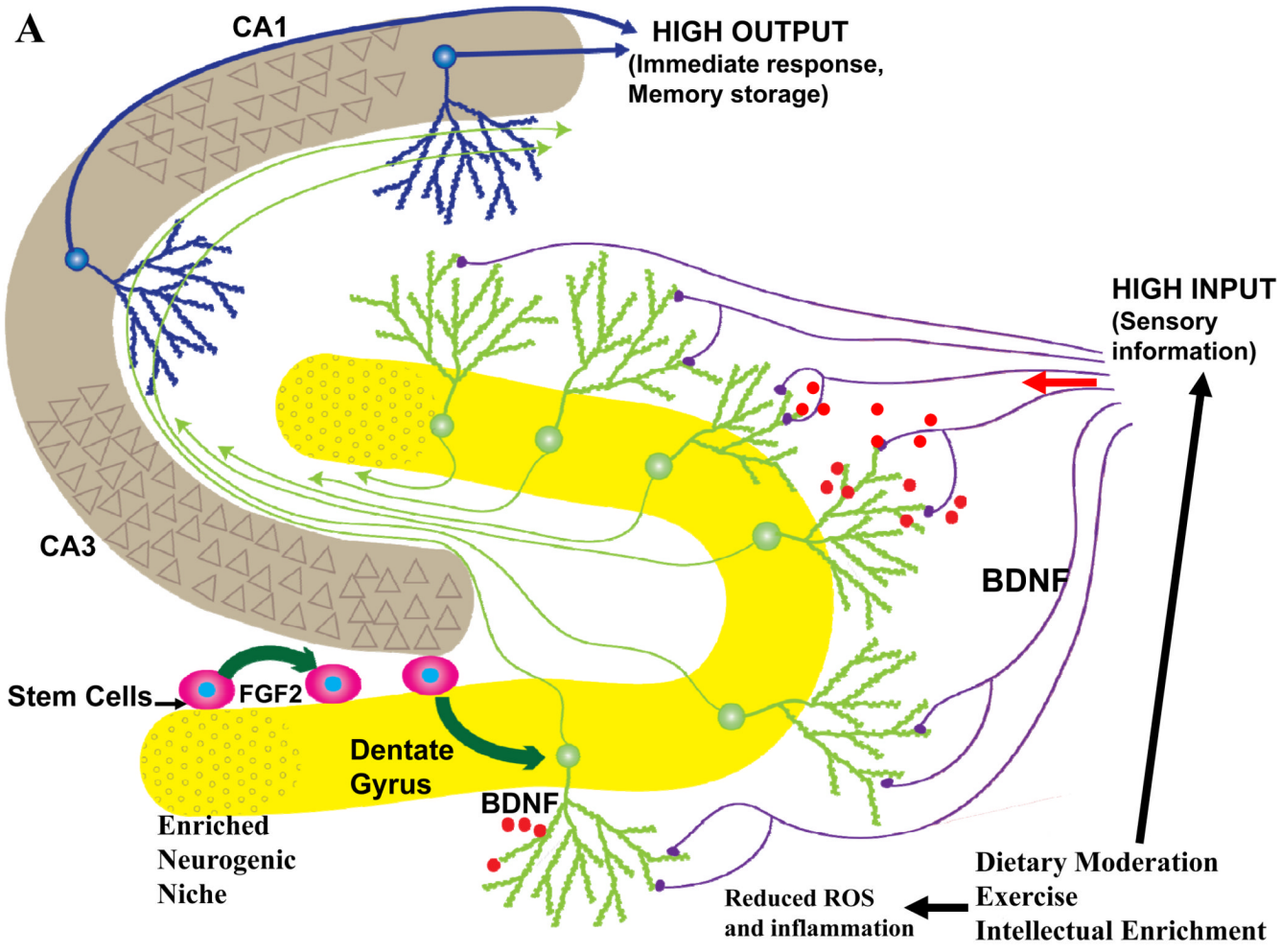


Figure 4.

Mechanisms of synaptic dysfunction in aging and Alzheimer's disease. The β-amyloid precursor protein is axonally transported and so is present in high amounts in presynaptic terminals. In properly functioning synapses the APP is proteolytically cleaved in the middle of the Aβ sequence by the α-secretase, thereby preventing the production of Aβ. During normal aging, and more so in AD, APP is cleaved at the N- and C-termini of Aβ by β-secretase and γ-secretase, respectively, resulting in the production and self-aggregation of Aβ. Aggregation of Aβ on the membrane generates ROS resulting in membrane lipid peroxidation, which then impairs the function of membrane ion-motive ATPases thereby promoting membrane depolarization and Ca^{2+} influx through NMDA receptor channels and voltage-dependent Ca^{2+} channels. Sustained elevation of cytoplasmic Ca^{2+} levels promotes depletion of presynaptic glutamate stores resulting in impaired synaptic transmission and damage to axons and dendrites. In addition, perturbed mitochondrial function caused by aging, oxidative stress and Aβ results in energy depletion in neurons which exacerbates synaptic dysfunction and degeneration of neurons. Further contributing to the demise of neurons in AD is dysregulation of endoplasmic reticulum (ER) function that results in depletion of ER Ca^{2+} stores and accumulation of misfolded proteins.



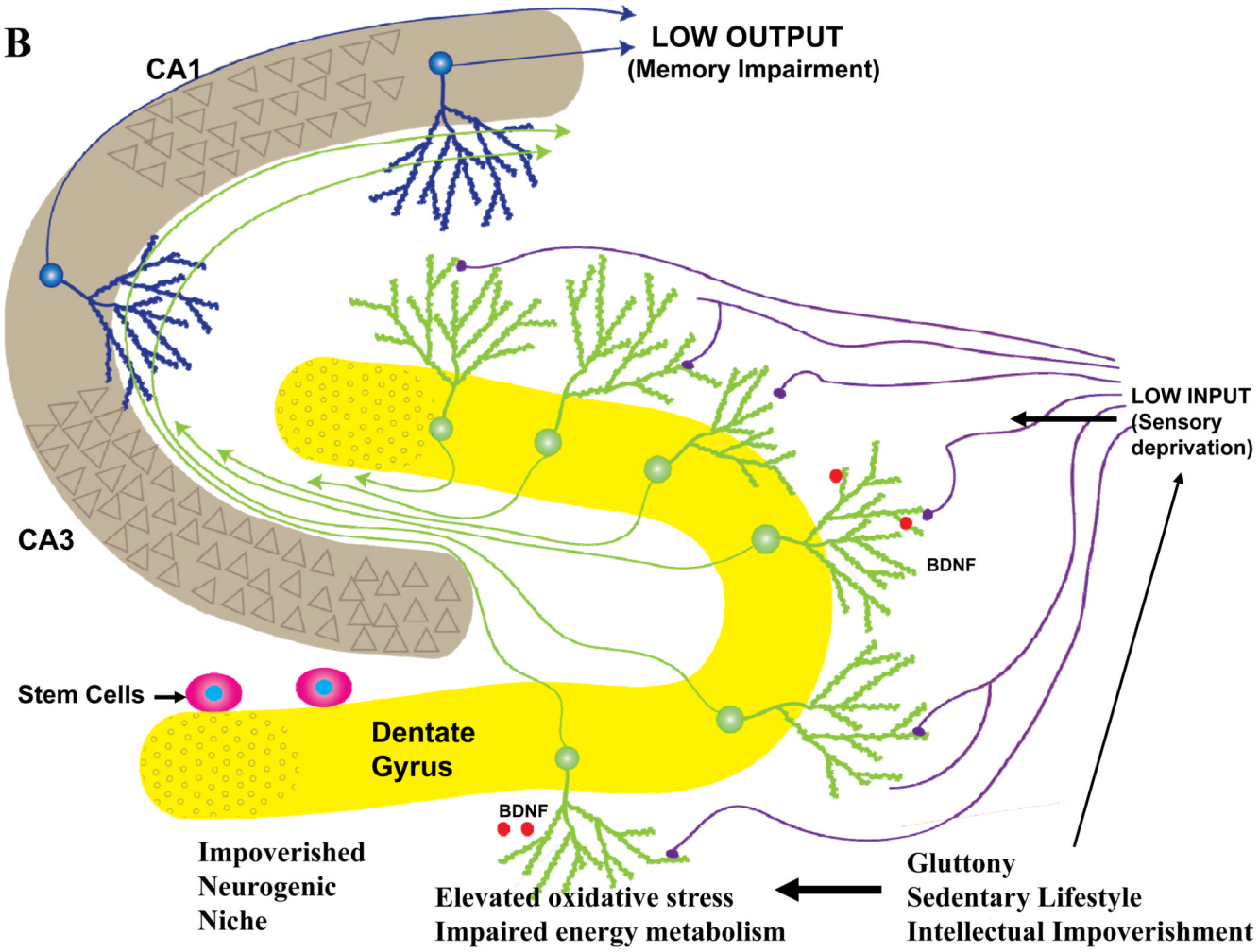


Figure 5.

The impact of lifelong 'brain healthy' and unhealthy lifestyles on late life hippocampal plasticity and cognitive function. Information from multimodal sensory association cortices enters the hippocampus from the entorhinal cortex via perforant path axons which synapse on dendrites of dentate granule neurons. The axons of granule neurons synapse on dendrites of pyramidal neurons which, in turn, may synapse on additional pyramidal projection neurons which then exit the hippocampus and innervate neurons in regions of the cerebral cortex involved in the long-term storage and processing of memories. **A.** Behaviors believed to promote healthy brain aging include moderation of dietary energy intake, regular exercise and engaging in intellectually challenging occupations and hobbies. Data suggest that these behaviors increase activity in hippocampal circuits and impose a mild cellular stress on neurons resulting in the activation of signaling pathways that induce the production of neurotrophic factors such as BDNF. As a consequence, synaptic plasticity and neurogenesis are enhanced and the resistance of neurons to aging and disease processes is increased. **B.** Behaviors that may contribute to cognitive impairment include excessive dietary energy intake, a sedentary lifestyle and a low level of cognitively challenging experiences. The latter lifestyle promotes diabetes and obesity, and can impair hippocampal synaptic plasticity and neurogenesis, thereby rendering neurons vulnerable to dysfunction and degeneration during aging.