Disrupted energy metabolism and neuronal circuit dysfunction in cognitive impairment and Alzheimer's disease

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Epidemiological, neuropathological, and functional neuroimaging evidence implicates global and regional disruptions in brain metabolism and energetics in the pathogenesis of cognitive impairment. Nerve cell microcircuits are modified by excitatory and inhibitory synaptic activity and neurotrophic factors. Ageing and Alzheimer's disease cause perturbations in cellular energy metabolism, level of excitation or inhibition, and neurotrophic factor release, which overwhelm compensatory mechanisms and result in dysfunction of neuronal microcircuits and brain networks. A prolonged positive energy balance impairs the ability of neurons to adapt to oxidative and metabolic stress. Results from experimental studies in animals show how disruptions caused by chronic positive energy balance, such as diabetes, lead to accelerated cognitive ageing and Alzheimer's disease. Therapeutic interventions to allay cognitive dysfunction that target energy metabolism and adaptive stress responses (such as neurotrophin signalling) have been effective in animal models and in preliminary studies in humans.

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Introduction

Several converging lines of evidence suggest a crucial 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 2 diabetes mellitus) in cognitive ageing[1] and Alzheimer's disease (AD).[2,3] Findings from studies using functional neuroimaging—including functional MRI (fMRI) and ^{18}F-fluorodeoxyglucose (FDG) PET—have shown regional metabolic changes associated with cognitive impairment.[4,5] Mitochondrial and metabolic alterations have been identified in the brains of cognitively impaired animals,[6–8] and abnormal cognition and neuronal changes[9–11] have been reported in the brains of metabolically impaired animals. By contrast, data from animal and human studies suggest that lifestyle alterations that improve global energy metabolism (such as calorie restriction and exercise) might be effective in preventing[12,13] or reversing[14,15] cognitive impairment and attenuating the atrophy[16,17] associated with brain ageing and AD.[18–20]

A separate line of research implicates brain network dysfunction in cognitive impairment. Complex cognitive functions and behaviours are a result of the brain's hierarchical organisation,[21] in which microcircuits of anatomically and functionally linked neurons interconnect to form large-scale brain networks.[22] The brain is organised in such a way that information processing occurs efficiently and economically in terms of metabolic costs,[23] which suggests that there is a fundamental link between brain energetics and network function. This suggestion is consistent with the fact that network dysfunction occurs in parallel with metabolic dysfunction during cognitive ageing and AD.[4,5,23]

How could brain network dysfunction be linked to global or regional energetic disruptions? Recent evidence has reinforced the idea that neurodegenerative diseases, in particular AD, preferentially target specific networks.[24–26] Within brain networks, a small number of nodes, so-called connector hubs, have a disproportionately high number of connections through which they integrate the functions of distant microcircuits.[26] Connector hubs are essential for information flow over a brain network; dysfunction of these hubs as a result of regional metabolic dysfunction secondary to neurodegenerative pathological changes can critically affect a network's function,[22] resulting in phenotypic changes in cognition and behaviour. Moreover, ageing alters the global processing of information and cognitive tasks by networks,[23] in parallel with global changes in brain metabolism.

Here, we review research on the relation between brain microcircuits and networks and the spread of AD against a background of ageing-related changes in energy metabolism. We assess evidence for adaptive changes in activation of microcircuits and networks in response to pathological processes—such as the balance of excitatory and inhibitory synaptic activity and neurotrophic factor production—and show how these adaptations affect regional neuroenergetics. Finally, we link these processes to whole-organism energetics and show how a positive energy balance caused by excessive calorie intake and a sedentary lifestyle favours cognitive ageing and the AD cascade by impairing adaptive responses.

Selective vulnerability in AD: connectivity and energetics

Imaging and histopathological evidence for a transcerebral spread of AD pathology

Neuroimaging research has established that manifestations of early AD result from specific network dysfunction caused by atrophy[27] and hypometabolism within critical nodes including the posterior cingulate, lateral temporal, lateral parietal, and medial lateral prefrontal cortices.[26,28] On MRI, atrophy in early AD is most evident in the medial temporal lobe (MTL), extending over time into the inferior temporal lobe, temporal pole, inferior parietal lobe, superior frontal lobe, posterior medial cortex (PMC, consisting of the posterior cingulate cortex and precuneus), inferior frontal

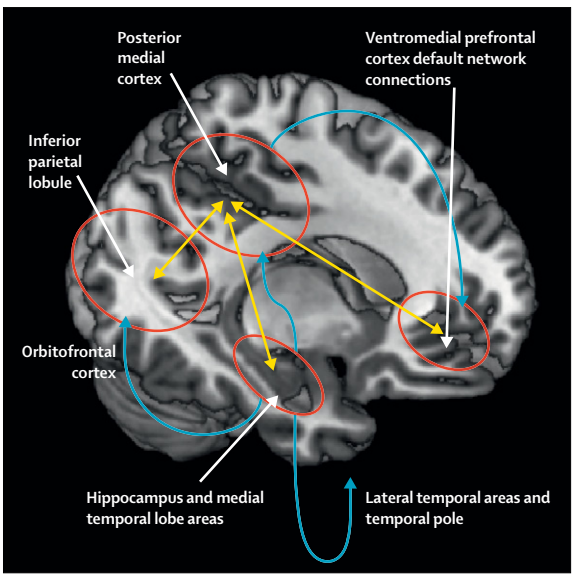

Figure 1: **Spread of neuropathology in Alzheimer's disease**
Neurofibrillary tangles and neurodegeneration first appear in the entorhinal cortex and then in other medial temporal lobe structures; fibrillary amyloid β deposits and plaques first appear in transmodal areas—such as the posterior medial cortex, the inferior parietal lobule, and the lateral temporal lobe and temporal pole—that maintain reciprocal connections (yellow arrows). All regions are shown with red circles. Spread of neurofibrillary tangles and neurodegeneration (blue arrows) is not associated with the spread of fibrillar amyloid β deposition and plaque formation.

lobe, and superior parietal regions.[29] Changes in hypometabolism on FDG-PET occur temporally in a similar regional pattern.[30] The early involvement of the parietal cortex is associated with a decrease in processing of visuospatial information,[31] whereas the early involvement of the MTL and PMC nodes of the episodic memory and default mode networks are responsible for major deficits in episodic and semantic memory in AD (figure 1). The causes of this selective regional vulnerability in AD are unclear. However, an increasing amount of evidence suggests that pathological changes spread into regions that are energetically challenged (regions with high levels of excitation under conditions of age-related and disease-related mitochondrial impairment and oxidative stress) and that receive neuronal projections from regions where pathological changes have already occurred.

We believe that a cohesive narrative for the temporal progression of AD must include a discussion of 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), which result in plaque formations; and intracellular neurofibrillary tangles (NFTs) consisting of hyperphosphorylated self-aggregating tau.[24,32,33] There are clear anatomical connections between sequentially affected areas in AD. Aβ deposition occurs at a consistently slow rate in various neocortical locations in some older individuals (figure 2).[34] Conversely, NFTs appear first in the subiculum and entorhinal cortex (layers II–III and layer IV) and are accompanied by synaptic and cellular loss.[24,32] The cells in layer II and adjacent parts of layer III that are affected by NFTs are characterised by a pattern of unique connectivity: they are those that receive lateral connections from the (transmodal) neocortex and project to the hippocampus proper or areas CA1–CA3.[24,35] Layer III neurons form the glutamatergic perforant pathway that terminates on distal dendrites of CA1 neurons, while layer II neurons project to CA3 pyramidal neurons, which give rise to the Schaffer collateral pathway that terminates on the apical dendrites of CA1 neurons. The loss of entorhinal neurons leaves the hippocampus without neocortical input[35] and directly impairs its function and plasticity.[36] By contrast, the affected cells in layer IV send lateral connections to the transmodal neocortex;[24] loss of these cells leaves the PMC and other transmodal cortices without hippocampal input.

The involvement of the neocortex in AD can be mostly attributed to its connectivity to the MTL allocortex; transmodal areas directly linked to the MTL are the most vulnerable, whereas motor and primary sensory areas that are not directly connected to it are least affected (figure 1).[24] This selective vulnerability is not attributable to cytoarchitecture: transmodal areas that are not directly linked to the MTL (such as the portion of anterior cingulate cortex that is linked to motor areas) are spared.[37] Moreover, absence of involvement of a brain region in AD does not imply resistance to neurodegenerative cascades in general, because frontoinsular and anterior cingulate areas are not affected in AD but degenerate in behavioural variant frontotemporal dementia.[38] A pattern of involvement that is similar to that found in the cortex is also present in the thalamus—Aβ deposits and NFTs are confined to nuclei with limbic connections—thus supporting the notion that connectivity determines regional variability in AD.[39]

Synaptic dysfunction mediates transneuronal spread of neurodegeneration

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 synapses,[40] where they affect the balance of excitation and inhibition,[41,42] impair long-term potentiation,[43] and facilitate long-term depression.[44,45] Axons and synapses are selectively vulnerable to intracellular accumulation of pathological substrates and might be the sites where the nerve cell death process starts.[46] Therefore, accumulation of Aβ oligomers in synapses might result in tau hyperphosphorylation and aggregation in axons, which might be transferred to the neuronal soma in the form of an NFT, far from the site of Aβ deposition.

Although 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 localisation might partly be accounted for by ageing and age-related

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metabolic diseases, which leave MTL neurons particularly vulnerable to the energetic stress associated with extracellular Aβ and intracellular tau deposits in AD. 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 the PMC and frontal and temporal transmodal nodes) compared with other brain regions.[23] Findings from animal studies have shown that hippocampal pyramidal neurons have the highest energy requirements of any neurons in the brain[47] and might therefore be at risk when metabolic needs are not met. Ageing-related cognitive impairment in rats is associated with down-regulation of insulin signalling and pathways that use glucose.[48] In hippocampal pyramidal neurons, ageing and chronic hyperinsulinaemia synergistically upregulate the gene for the glucocorticoid receptor and genes for inflammatory or immune pathways and downregulate insulin signalling genes, thereby blocking glucose use and decreasing mitochondrial function.[6] The end result of chronic hyperinsulinaemia is MTL atrophy.[49]

Regarding affected neocortical areas, the PMC and medial prefrontal hubs of the default mode network show early functional impairment in AD,[5,50] which is associated with Aβ deposition.[51,52] We believe that this vulnerability is the result of the recruitment of these hubs to compensate for deteriorating hippocampal function with ageing 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 impairment,[53] and successful memory encoding can be maintained only by hippocampal hyperactivation. Similarly, in ageing and early AD, increased activation of the hippocampus, PMC, and frontal areas is required for successful memory retrieval.[54,55] This increased hippocampal recruitment presumably leads to a chronic increase in the energy requirements of hippocampal neurons. With AD progression (clinically at the stage of late mild cognitive impairment [MCI]), PMC deactivation is further attenuated during encoding of memory,[56] especially among *APOE ε4* carriers, suggesting that this deactivation is a part of AD pathophysiology. Whenever the brain is not engaged in specific cognitive tasks, unrestrained episodic retrieval and semantic processing occur, representing the so-called default functional state of the brain; this lack of deactivation causes a chronic increase in the energy requirements of default network connector hubs, such as the PMC. Eventually, atrophy caused by neuronal death occurs in affected default mode network nodes, resulting in severe hypometabolism.[28]

Excitatory and inhibitory signalling dysregulation in ageing and AD

Much of the energy that neurons use is for synaptic signalling;[57] thus, neuronal energetics are linked to neurotransmission. Most of the brain's neurons and

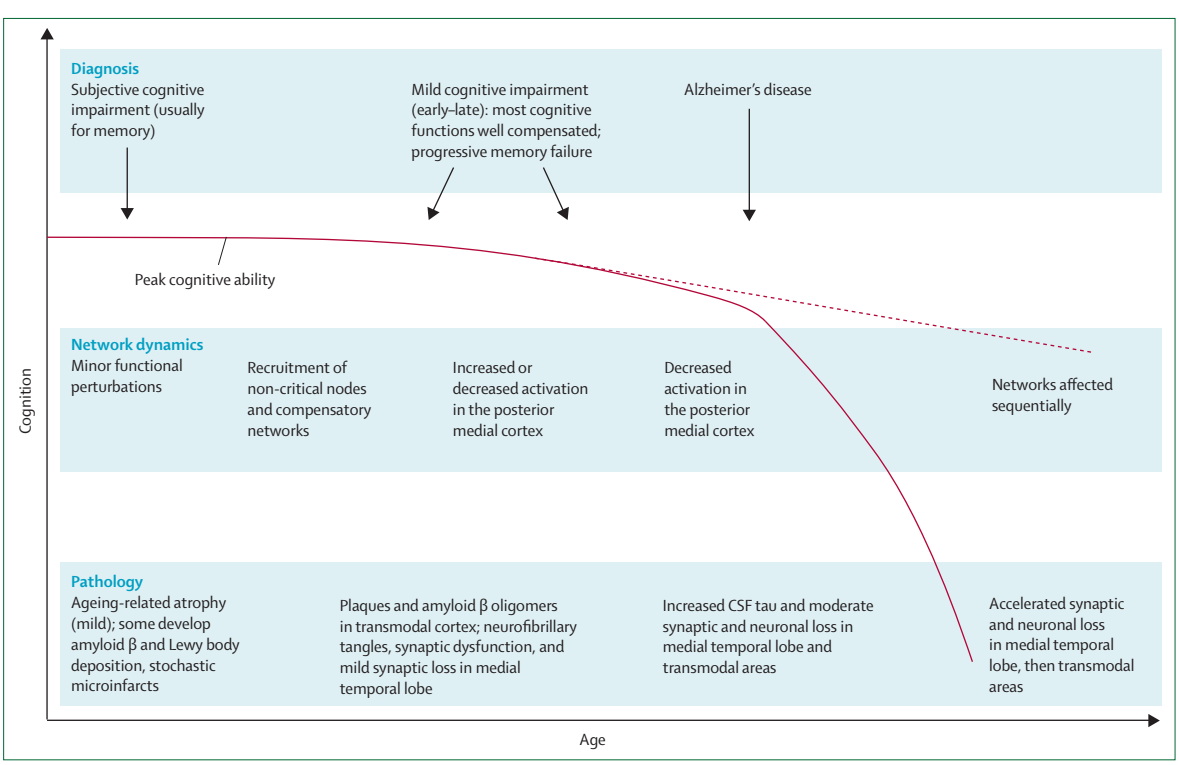

Figure 2: **Changes in cognitive ability with age in the presence or absence of Alzheimer's disease pathology**
Schematic progression of pathology, brain network dynamics, and clinical manifestations.

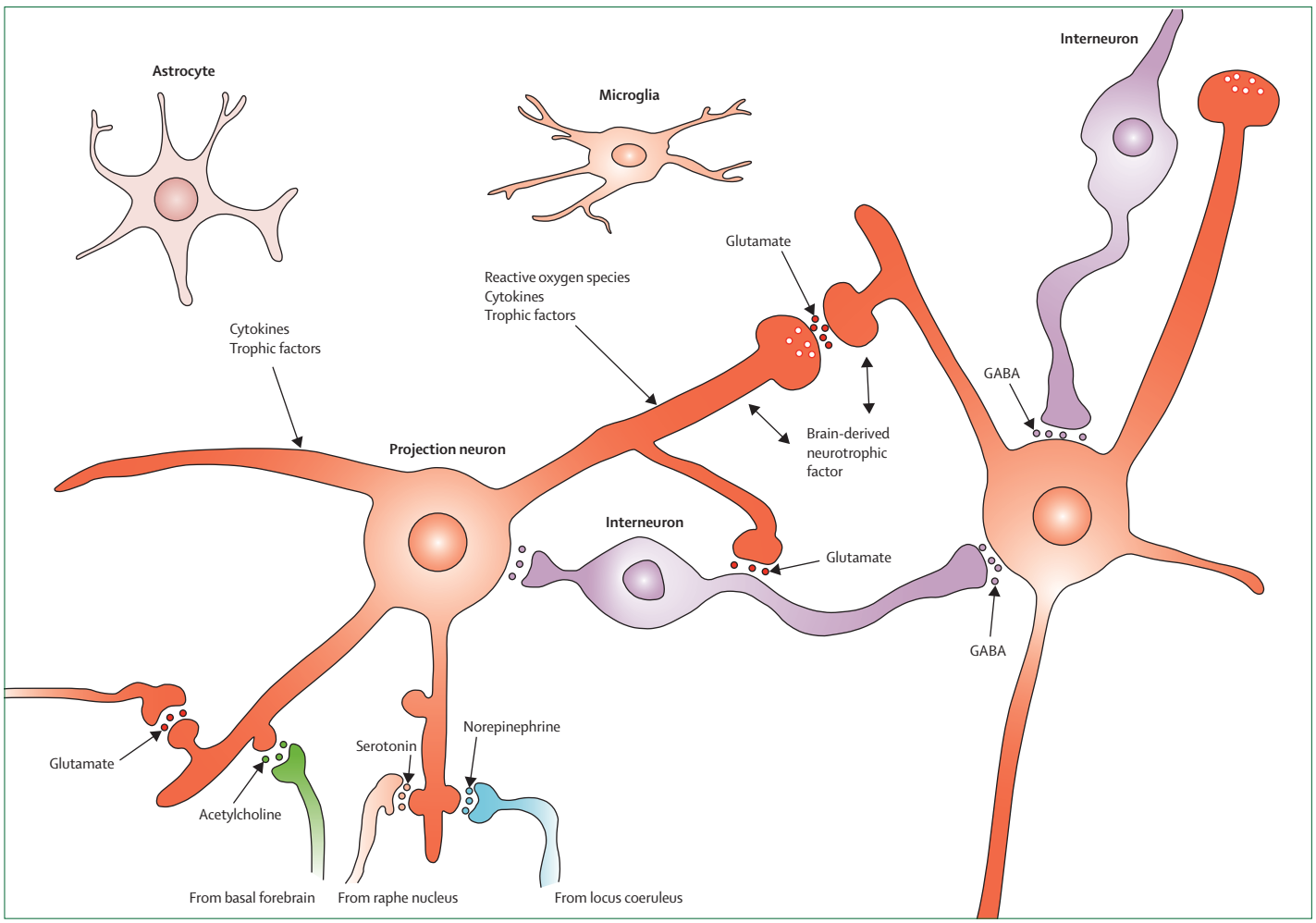

Figure 3: **Basic organisation of neuronal microcircuits involved in cognitive processing**
The major excitatory projection neurons are glutamatergic and their axons synapse onto dendrites of other glutamatergic neurons that might, in turn, project their axons to a different brain region. GABAergic interneurons 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 neurons modulated by norepinephrine, serotonin, and acetylcholine. The cell bodies of these neurons are located in the locus coeruleus, 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 that might normally be important in synaptic plasticity. However, excessive production of proinflammatory cytokines and reactive oxygen species by glial cells has been implicated in the pathogenesis of cognitive impairment and Alzheimer's disease.

synapses release either glutamate or GABA, whereas other neurotransmitters (serotonin, norepinephrine, dopamine, and acetylcholine) and neuropeptides (eg, somatostatin, corticotrophin-releasing hormone, and neurokinins) fine tune the activity in neural networks.[58] Nerve cell microcircuits within different brain regions are organised in a similar way (figure 3). Glutamate released from presynaptic terminals activates AMPA receptors, resulting in depolarisation of the postsynaptic membrane and calcium influx through NMDA receptor channels and voltage-gated calcium channels (figure 4). Calcium acts as a second messenger and activates cascades of enzymes (protein kinases, nitric oxide synthase, and proteases) and transcription factors (eg, cAMP response element-binding [CREB] protein and activator protein 1) that mediate rapid or delayed biochemical and structural changes and might also increase the resistance of the neurons to disease. Perturbations in the balance between glutamatergic and GABAergic signalling occur early in the development of age-related cognitive impairment and AD and result from and contribute to disrupted cellular metabolism. Moreover, normal synaptic activity reduces Aβ production and protects synapses against Aβ-related alterations.[59]

Inhibitory imbalances (induced by GABA receptor agonists or glutamate receptor antagonists) impair synaptic plasticity and associated learning and memory processes in animals and people.[60] Conversely, excitatory imbalance caused by excessive glutamate receptor activation or reduced GABAergic signalling, or both, can result in seizures and degeneration of synapses and neurons.[61] Complex microcircuit alterations that affect regional excitatory or inhibitory balance occur in the hippocampus and cortex in ageing and AD. Findings

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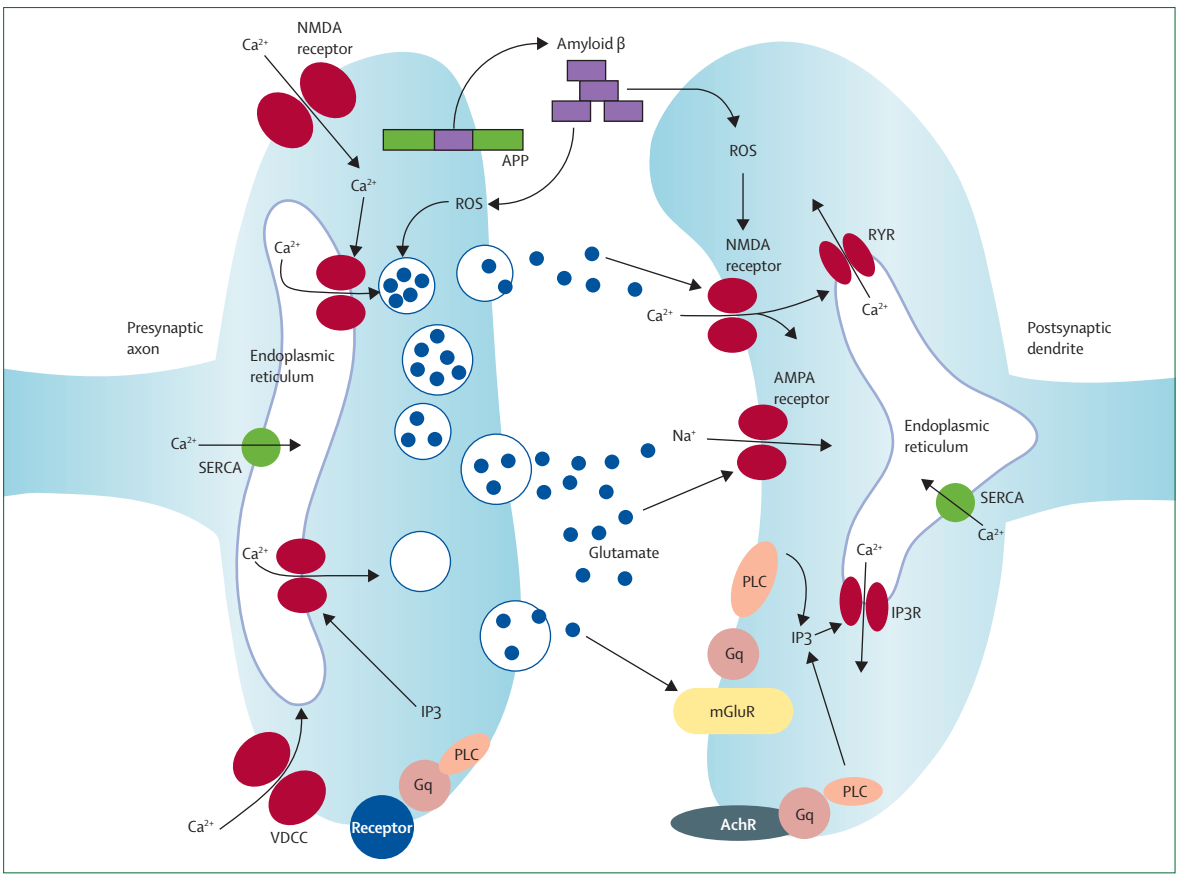

Figure 4: **Mechanisms of synaptic dysfunction in ageing and Alzheimer's disease**
APP is axonally transported and so is present in high concentrations in presynaptic terminals. In properly functioning synapses, APP is proteolytically cleaved in the middle of the amyloid β sequence by α secretase, thereby preventing the production of amyloid β. During normal ageing, and more so in Alzheimer's disease, APP is cleaved at the N-terminal and C-terminal of amyloid β by β secretase and γ secretase, respectively, resulting in the production and self-aggregation of amyloid β. Aggregation of amyloid β on the membrane generates ROS, which results in membrane lipid peroxidation. This in turn impairs the function of membrane ion-motive ATPases, thereby promoting membrane depolarisation and calcium influx through NMDA receptor channels and voltage-dependent calcium channels. Sustained increases in cytoplasmic calcium concentrations promote depletion of presynaptic glutamate stores, resulting in impaired synaptic transmission and damage to axons and dendrites. Additionally, disrupted mitochondrial function caused by ageing, oxidative stress, and amyloid β results in energy depletion in neurons, which exacerbates synaptic dysfunction and degeneration of neurons. Dysregulation of endoplasmic reticulum function, which results in depletion of endoplasmic reticulum calcium stores and accumulation of misfolded proteins further contributes to the death of neurons in Alzheimer's disease. APP=amyloid precursor protein. ROS=reactive oxygen species. SERCA=sarco/endoplasmic reticulum Ca^{2+}-ATPase. RyR=ryanodine receptor. IP3R=inositol trisphosphate receptor. PLC=phospholipase C. mGluR=metabotropic glutamate receptor. AchR=acetylcholine receptor. VDCC=voltage-dependent calcium channel.

from studies in animals have shown that ageing decreases GABAergic signalling in the hippocampus,[62] resulting in excitatory imbalance, while at the same time ageing impairs neuronal glucose uptake, causes mitochondrial dysfunction, and activates glucocorticoid pathways,[6] which makes neurons vulnerable to glutamate-induced damage.[63] The excitatory imbalance of ageing might be exacerbated by AD, because Aβ promotes membrane depolarisation and makes human cortical neurons vulnerable to glutamate-mediated calcium overload in vitro,[64] which might lead to the emergence of hyperactive neuronal clusters close to plaques, as has been reported in a mouse model of AD.[42] These clusters might cause the increased metabolism in nodes of the default mode network that is associated with high regional Pittsburgh compound B binding on PET imaging and which occurs transiently in AD before atrophy.[28] Excitatory imbalance in AD might also result in an increased occurrence of epilepsy.[65] However, AD can also cause a regional inhibitory imbalance: hippocampal synaptic plasticity is impaired in mouse models of AD because of reduced NMDA receptor activity,[66] whereas Aβ can reduce seizure-like activity induced by GABA receptor antagonists in hippocampal neurons in culture.[67] To resolve these apparent disparities, 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 that encode proteins involved in the regulation of neuronal excitability is altered in brain ageing and AD. Age-related modifications of gene

promoter regions are associated with reduced expression of genes that encode proteins involved in synaptic plasticity (eg, glutamate and GABA receptor subunits and synaptic vesicle proteins) and cellular calcium homoeostasis (calcium binding proteins, calcium-dependent kinases, and calcium transporters) in man.[68] Alterations in the expression of genes involved in synaptic plasticity and regulation of calcium metabolism have been reported in animal models of ageing and AD and in older people.[69,70] The downregulation of inhibitory signalling and calcium binding proteins might make neurons vulnerable to calcium overload. Chronic experimental silencing of cortical neurons in vitro results in molecular changes similar to those seen in ageing and AD, including reduced expression of genes involved in GABAergic transmission, inhibitory neuropeptides, calcium buffering, and signalling mediated by calmodulin and CREB protein.[71]

The events downstream of disrupted network activity and dysregulated cellular energy metabolism that lead to neuronal death might 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 ageing.[72] Physiological levels of glutamate receptor activation upregulate expression of DNA repair genes[73] and induce the movement of proteasomes from dendritic shafts into synaptic spines,[74] protecting them against the accumulation of damaged DNA and proteins. Nerve cell microcircuit perturbations in AD might impair these processes.

Neurotrophic factors produced by neurons or glial cells are important for survival and growth of neurons. Brain-derived neurotrophic factor (BDNF) is produced by neurons throughout the brain and is released in an activity-dependent manner (figure 5).[75] BDNF is important in synaptic plasticity, learning and memory, and neuro-genesis, and can protect neurons against metabolic and oxidative damage.[46] Additionally, BDNF enhances intracellular energy (ATP and NAD^+) availability to cultured mouse neurons by increasing expression of glucose transporters and stimulating aminoacid transport.[76] Findings from studies of transgenic mouse models of AD suggest that large Aβ oligomers suppress BDNF production,[77] disrupt its ability to activate CREB protein,[78] and block the retrograde trafficking of BDNF from synaptic terminals to the nucleus, which impairs its ability to promote neuronal survival.[79] Selective blockade of NMDA receptors mimics the abnormal molecular phenotypes of electrically silenced neurons,[71] and treatment with BDNF reverses the perturbations caused by chronic suppression of neuronal activity.[71] These findings suggest that activity-dependent neurotrophic signalling is impaired in brain ageing and AD. Indeed, BDNF in the CSF decreases in people during ageing and even more so in patients with AD.[80]

Molecular alterations in AD and disrupted neuronal energy metabolism

Aβ oligomer formation in neuronal rat cultures generates hydrogen peroxide and hydroxyl radicals, which then induce lipid peroxidation in the plasma membrane of neurons and glial cells and impair the function of ion-motive (calcium, sodium, and potassium) ATPases and glucose transporters; as a result, cellular calcium and energy homoeostasis are disrupted and synaptic function is impaired (figure 4).[81] Additionally, AD pathogenesis might be linked to excessive accumulation of calcium in the endoplasmic reticulum, which contributes to synaptic dysfunction and neuronal degeneration.[82] In-vivo imaging of intracellular calcium concentrations in cortical neurons in a mouse model of AD showed that some neurons are hypoactive whereas neurons close to Aβ plaques are hyperactive.[42] These findings are consistent with the excitoxicity and energy depletion hypothesis of neuronal degeneration in AD.[46]

Impairment of mitochondrial function occurs in neurons in MCI and AD and probably results from a combination of factors including Aβ oligomer accumulation, oxidative stress, and a deficit in neurotrophin signalling.[83] The activity of several mitochondrial enzymes (eg, α-ketoglutarate, pyruvate, and isocitrate dehydrogenases) is reduced in brain tissue samples from patients with AD,[84] and experimental findings in animal models of ageing 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 and are important in local calcium signalling and associated processes that are involved in synaptic plasticity.[83,85] These mitochondria might be particularly vulnerable to neuronal network dysfunction and so might be damaged early in AD.

Disrupted cellular energy metabolism and associated oxidative stress are also involved in the hyperphosphorylation and self-aggregation of tau. In a mouse model of Down's syndrome with a subset of triplicated human chromosome 21 orthologue genes (including amyloid precursor protein), mitochondrial membrane potential and ATP production are reduced in brain cells and tau is hyperphosphorlyated because of an increase in activity of glycogen synthase kinase 3β (GSK3β) and c-Jun N-terminal kinase.[86] Among the many kinases that can phosphorylate tau, data from mouse models of AD strongly implicate GSK3β in the pathogenesis of AD.[87] GSK3β might have important roles in Aβ processing[88] and in linking disrupted cellular energy metabolism to cognitive decline in ageing and AD. Drugs that inhibit GSK3β reduce tau hyperphosphorylation, enhance cognitive function, and reduce Aβ production in mouse models of AD.[89] In rat cell lines, GSK3β suppression improves glucose uptake by several cell types,[90] and in a mouse model of AD, GSK3β suppression increased brain insulin-like growth factor 1 (IGF-1).[91] These data suggest an important link between AD pathogenesis and

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brain energy metabolism that is amenable to pharmacological interventions.

Effect of energy intake and expenditure on cognitive ageing

High-energy diets and diabetes might have adverse effects on cognitive function in ageing and AD, whereas dietary energy restriction might have beneficial effects (figure 5). Here, we discuss experimental data in animals that support these claims. In rhesus monkeys, ageing is associated with decreased number (or activity) of functional mitochondria in the hippocampus, and a negative association exists between severity of metabolic syndrome and oxidative function of these mitochondria.[6] Rodents fed with fats or simple sugars exhibit poor learning and memory compared with animals on lower energy diets,[9] and even in young animals excessive weight impairs some cognitive domains.[10] Conversely, in a mouse model of accelerated ageing, calorie restriction attenuated age-related deficits in learning and memory.[92] Lifelong calorie restriction in mice prevents age-related decline in learning[93] and preserves spatial, non-spatial, and working memory in aged rats.[94] Even when started in midlife, dietary energy restriction preserves cognitive functions in ageing mice.[95] In mouse models of AD, high-energy diets exacerbate Aβ deposition and memory impairment,[96] whereas dietary energy restriction prevents[97] or attenuates[98] the development of cognitive impairment and Aβ and tau pathologies.

Three 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 increased in brain cells of animals on high-energy diets[99] and reduced in animals on low-energy diets.[100] High-energy diets promote inflammatory processes in the brain that are associated with cognitive impairment.[101] Conversely, dietary energy restriction protects neurons and synapses in animal models in which neurotoxicity is mediated by oxidative stress.[102] Fasting on alternate days reduced brain damage and improved functional outcome in an animal model of stroke by a mechanism involving suppression of brain inflammation.[103] The effectiveness of dietary restriction was less in older animals than in younger animals, perhaps as a result of age-related impairment of adaptive cellular stress response pathways.[103]

Emerging evidence suggests that excessive dietary energy intake impairs[101] and dietary energy restriction increases BDNF signalling.[103] Findings from animal studies in which BDNF or its receptor trkB have been genetically manipulated, or BDNF has been administered to the brain, have shown major roles for BDNF in synaptic plasticity, learning and memory, and neuronal resistance to oxidative, metabolic, and excitotoxic insults that are associated with cognitive dysfunction and AD.[46] BDNF

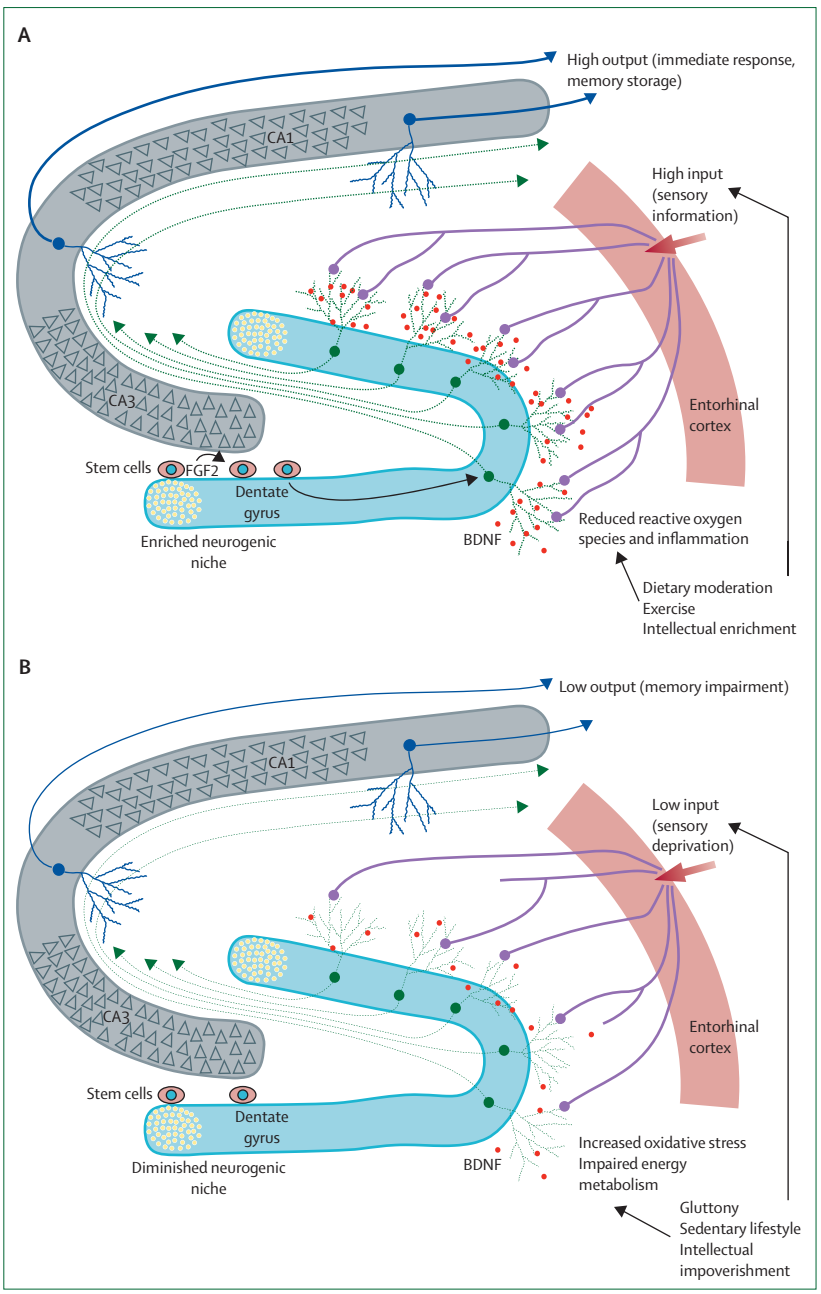

Figure 5: **The effect of lifelong healthy and unhealthy lifestyles on late life hippocampal plasticity and cognitive function**

Information from multimodal sensory association cortices enters the hippocampus from the entorhinal cortex via the perforant path axons, which synapse onto dendrites of dentate granule neurons. The axons of granule neurons synapse onto dendrites of pyramidal neurons, which, in turn, could synapse onto 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) Behaviours believed to promote healthy brain ageing include moderation of dietary energy intake, regular exercise, and engaging in intellectually challenging occupations and hobbies. These behaviours increase activity in hippocampal circuits and cause mild cellular stress on neurons, which results in the activation of signalling pathways that induce the production of neurotrophic factors such as BDNF. As a consequence, synaptic plasticity and neurogenesis are increased and the resistance of neurons to ageing and disease processes is increased. (B) Behaviours that might contribute to cognitive impairment include excessive dietary energy intake, a sedentary lifestyle, and a low level of cognitively challenging experiences. The latter lifestyle can lead to diabetes and obesity, and can impair hippocampal synaptic plasticity and neurogenesis, thereby leaving neurons vulnerable to dysfunction and degeneration during ageing. FGF2=fibroblast growth factor 2. BDNF=brain-derived neurotrophic factor. Adapted from Lazarov et al,[75] by permission of Elsevier.

also increases neurogenesis in the hippocampus, which might contribute to maintenance of hippocampal neurons and preservation of cognitive function during ageing.[104] Leptin receptor mutant diabetic mice that have reduced BDNF concentrations exhibit cognitive impairment and impaired synaptic function and neurogenesis.[11] BDNF signalling is also involved in energy metabolism and cognitive function in humans; people with BDNF haploinsufficiency[105] and with de-novo trkB mutations[106] are obese, insulin resistant, and cognitively impaired.

Impaired cellular energy metabolism occurs with increased oxidative stress, as shown by reduced expression or activity of mitochondrial proteins and oxidative genomic damage.[107] 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 can impair cognitive function, partly by hyperactivation of the hypothalamic–pituitary–adrenal axis, and lowering glucocorticoid concentrations can restore cognitive function, synaptic plasticity, and neurogenesis.[11] The links between diabetes and AD are complex and probably also involve inflammatory mechanisms; in double-mutant transgenic and diabetic mouse models of AD, the onset of diabetes exacerbates AD-like cognitive dysfunction without an increase in brain Aβ burden but in association with cerebrovascular inflammation.[108]

Benefits of exercise on cognitive function have been reported during normal ageing and in models of insulin resistance or diabetes and AD in animal studies, and the underlying mechanisms of these benefits have been elucidated (figure 5). Several studies have reported beneficial effects of exercise in mouse models of AD, such as improved cognitive performance.[18] Exercise reduces glucocorticoid concentrations and increases hippocampal neurogenesis.[19] Mild metabolic challenges associated with exercise induce the expression of genes that encode proteins that increase the ability to resist perturbations and cellular plasticity, thus improving learning. During exercise in rats, concentrations of proteins involved in cellular energy metabolism and synaptic plasticity are increased in the hippocampus.[20] The hippocampal transcriptomes of old mice that have been regularly running in a wheel throughout their lives have greater learning-induced activation of synaptic plasticity and mitochondrial function genes, and oxidative stress and lipid metabolism genes are downregulated;[109] running also modulates genes involved in cell excitability, energy metabolism, and insulin signalling.[109] Exercise affects cognition by improving learning, which might explain why some studies have failed to show a beneficial effect of exercise on cognition independent of cognitive stimulation.[110]

BDNF plays a pivotal part in the cellular and molecular mechanisms underlying the cognition-enhancing effects of exercise. Even short-term exercise can improve memory in rats and is associated with increased hippocampal BDNF concentrations.[111] Exercise and calorie restriction increase hippocampal dendritic spine density and BDNF concentrations in diabetic mice and exercise significantly enhances the effect of calorie restriction on spine density and BDNF concentrations.[112] Exercise-induced BDNF production and release might strengthen existing synapses, promote synaptogenesis, and stimulate neurogenesis.[19,46] The effects of exercise do not always occur simultaneously across cognitive domains; instead, memory retention seems to be best immediately after exercise, and is associated with increased BDNF concentrations, whereas memory acquisition is improved after exercise after a delay.[113] A second crucial mediator of the brain effects of exercise is peripherally produced IGF-1, which induces plastic and neuroprotective brain changes and stimulates hippocampal neurogenesis.[114] Finally, two proteins that are important in cognitive processes—mitogen-activated protein kinase and the transcription factor CREB—are also increased in the hippocampus of rats in response to exercise.[115]

Energy-based therapeutic interventions in cognitive ageing and AD

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

The substantial evidence that diabetes is a risk factor for cognitive impairment and AD has led to preclinical studies aimed at establishing the efficacy of antidiabetic treatments in animal models.[94,97,116] At the cellular level, insulin decreases binding of Aβ oligomers at the synapses and thus decreases the oxidative stress and synaptic spine deterioration caused by the oligomers.[117] Several small studies have suggested that insulin treatment improves cognitive function in patients with MCI or AD. In one study, patients with diabetes and coincident AD who were treated with subcutaneous insulin had significantly less cognitive decline compared with placebo-treated patients.[118] In another study, intranasal insulin improved cognition in patients with AD.[119] However, not all trials of drugs that target insulin signalling have reported benefits; the insulin-sensitising drug rosiglitazone did not improve cognitive function in a 6-month trial in patients with mild-to-moderate AD.[120] Particularly promising for the treatment of cognitive impairment and AD, especially in insulin-resistant patients, are the glucagon-like peptide 1 (GLP-1) receptor agonists. GLP-1 receptors are widely expressed in neurons throughout the brain and data suggest that their activation increases synaptic plasticity and cognitive performance and promotes neuronal survival.[121] Recent preclinical studies have reported

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beneficial effects of GLP-1 receptor agonists in animal models of AD, including protective and restorative effects on synaptic plasticity and cognitive function.[116,122] Similarly, in a mouse model of AD, treatment with sitagliptin (which inhibits the enzyme that inactivates GLP-1 in the blood, DPP4) resulted in increased concentrations of GLP-1 in the brain, ameliorated memory deficits, and reduced oxidative stress.[123] A protease-resistant analogue of GLP-1, exendin-4, is widely used for treatment of diabetes.[121] Clinical trials to test the efficacy of exendin-4 in people with MCI or early AD have recently been started because of the drug's dual actions on glucose metabolism and neurons affected in AD.[124]

Because of their multiple neuroprotective actions, neurotrophic factors such as nerve growth factor (NGF) and BDNF have great potential as therapeutic drugs for AD, as well as against ageing-related cognitive decline. Unfortunately, neurotrophic factors exert pleiotropic effects and delivery at the site of pathology is difficult. Therefore, small molecules selectively targeting specific neurotrophin receptors show greater promise for modulating neurotrophin signalling via systemic delivery.[125] An alternative approach to selective targeting by small molecules is gene therapy. Intraparenchymal NGF gene delivery to the basal forebrain of aged rhesus monkeys restores concentrations of cholinergic neuronal markers to levels found in young monkeys,[126] whereas NGF gene transfer into the septum of aged rats increased the number of cholinergic neurons and amount of acetylcholine release.[127] NGF and recombinant hNGF-61 were successfully delivered by ocular and intranasal administration to transgenic mouse models of AD and suppressed AD pathology.[128,129] In aged rats and non-human primates, local BDNF delivery reverses neuronal atrophy and ameliorates age-related cognitive impairment, whereas in transgenic mouse models of AD, BDNF gene delivery reverses synapse loss, partially normalises aberrant gene expression, improves cell signalling, and restores learning and memory.[130]

Finally, there is potential for sustaining and restoring functional circuits in the ageing brain by providing neurons with chemicals that increase concentrations of ATP and nicotinamide adenine dinucleotide (NAD+). Best known for its ability to preserve ATP concentrations in muscle cells and thus improve endurance, creatine can also protect neurons against oxidative and metabolic damage, including Aβ toxicity, in vitro[131] or against traumatic brain injury in vivo.[132] Administration of nicotinamide, which increases cellular NAD+ concentrations in the brain, improved cognitive function in old rats[133] and in a mouse model of AD.[134] Preliminary studies in humans suggest that dietary niacin, which consists of nicotinamide and nicotinic acid, can reduce the risk of age-related cognitive decline and AD.[135] Another approach to improving neuronal bioenergetics is to target mitochondrial potassium channels; cognitive function is improved and Aβ and tau pathologies are decreased in AD mice treated with the mitochondrial potassium channel opener diazoxide.[136] Because creatine, nicotinamide, and diazoxide are all approved for use in humans, clinical trials in patients with MCI and AD could be started without delay.

Search strategy and selection criteria

We searched PubMed (January, 1990, to September, 2010) with various combinations of the following terms: "Alzheimer", "cognitive", "energy metabolism", "network, excitatory", "GABA", "glutamate", "amyloid", "mitochondria", "neurotrophic factors", "diabetes", "exercise", and "oxidative stress". References from identified studies were also checked. Only articles published in English were included. The final list of references was chosen to include papers that we judged to report key findings in leading journals. Additionally, we aimed to cite at least two references (from different laboratories) to support our conclusions.

Conclusions

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 enrichment cannot, in our view, be overstated. The available evidence suggests that these three brain-healthy habits protect cells against the effects of ageing and AD by activating cellular stress response pathways that induce the expression of genes that encode proteins involved in cytoprotection and synaptic and neurogenic plasticity (figure 5). Such brain-healthy habits should be encouraged. Novel patterns of food intake might be considered in light of recent evidence that alternate day calorie restriction diets can be adhered to and could lead to improved health,[137] although further research is needed before such approaches should be recommended. Finally, from the perspective of drug discovery for AD, we propose an alternative focus to Aβ metabolism—to a focus on the levels of whole body and cellular energy metabolism and stimulation of adaptive cellular stress responses. Pharmacological approaches should also focus on targets such as drugs that suppress inflammation or improve mitochondrial function.[138] Whether these changes are going to be successful in preventing and treating cognitive ageing and AD is an open question and a challenge.

Contributors

DK and MPM organised and wrote the manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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