The Neuroinflammation and Loss of Hippocampal GABAergic Interneurons That Mediate Age-Related Decline in Cognitive Function May be Interdependent

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Abstract

Current efforts to explain the moderate cognitive decline associated with "healthy aging" focus on two key mechanisms: an age-related loss of GABAergic interneurons in the hippocampus and cortex, likely mediated by increased neuronal oxidative stress; and neuroinflammation, reflecting an increased activation of brain microglia which produce pro-inflammatory hormones, most notably interleukin-1, capable of impairing hippocampal long-term potentiation. It is proposed that these two mechanisms are functionally linked. Activated microglia produce interleukin-6, which stimulates NADPH oxidase overexpression in GABAergic neurons, and hence renders them vulnerable to excitotoxic death. In turn, the die off of these neurons may break a homeostatic feedback loop, dependent on endocannabinoid signaling, which helps to control microglial activation. Whether or not this formulation is valid, there is reason to suspect that a number of nutraceuticals, drugs, or lifestyle measures have potential for slowing cognitive aging by dampening microglial activation and/or aiding survival of forebrain GABAergic neurons. Measures which suppress microglial activation are of particular interest, in that they might be expected to have a relatively acute beneficial impact on cognitive function in the elderly. Agents or measures with credible potential for slowing cognitive aging are briefly cited, and include taurine, centrally-effective antioxidants (such as spirulina, astaxanthin, N-acetylcysteine, melatonin), phase 2 inducers and flavonoids (notably lipoic acid, EGCG, fisetin, and anthocyanins), pterostilbene, DHA, vitamin D, brain-permeable angiotensin II antagonists, berberine, sildenafil or icariin, cannabinoids, physical and mental exercise training, a diet low in saturated fat and rich in fruits and vegetables, and moderate calorie restriction. Many of these measures – notably those which quell neuroinflammation – might also slow the onset of common neurodegenerative disorders such as Parkinson's or Alzheimer's. Optimal preservation of cognitive function in the elderly will of course also require adjunctive measures – including pharmaceutical control of hypertension, a diet rich in potassium and moderate in sodium, exercise training, weight control – that help to maintain cerebrovascular health and prevent stroke.

Loss of Hippocampal GABAergic Interneurons Promotes Age-Related Cognitive Decline

The mechanisms which underlie the decline in optimal cognitive capacities associated with "healthy aging" – independent of stroke or chronic cerebral ischemia, Alzheimer's disease (AD), or other neurodegenerative disorders – are undoubtedly extremely complex and multifactorial. Nonetheless, recent rodent research suggests that two phenomena may be of key importance in this regard. And, as we shall see, there is reason to suspect that they may be functionally related.

One recent line of research points to a gradual loss of GABAergic inhibitory interneurons in the forebrain[1-5] – hippocampus and cortex – as a major contributor to age-related cognitive decline. Dugan and colleagues have recently demonstrated that the loss of parvalbumin-positive hippocampal

GABAergic neurons is mediated by an age-related rise in IL-6.[5] There is considerable evidence that IL-6 levels tend to rise with age both systemically and in the brain, and this rise has long been suspected to play a key mediating role in age-related loss of functional capacities.[6, 7] Dugan's group demonstrated that, in C56BL6 mice that were genetically IL-6 deficient (IL-6^{-/-}), the age-related loss of forebrain GABAergic neurons did not occur. Moreover, the age-related cognitive dysfunctions typically seen in this strain were substantially though not wholly ameliorated in the IL-6 knock-out mice; the knockout mice at 22 months of age were notably superior to controls of comparable age in 3 tests evaluating hippocampus-dependent learning and memory (novel object recognition, Barnes maze, and Morris water maze). These studies also established a probable basis for the IL-6-driven loss of these GABAergic neurons: IL-6 induces increased expression of Nox-2-dependent NADPH oxidase activity in these neurons, an effect mediated at least in part by NF-kappaB activation. Speculating that oxidant-mediated excitotoxicity was responsible for the die-off of GABAergic neurons, the researchers proceeded to demonstrate that daily treatment of wild-type C56BL6 mice from age 12 months with a superoxide dismutase-mimetic drug, C3, was associated with a partial conservation of learning and memory capacities in 22 month-old mice, comparable to that seen in the IL-6 knockout mice. These findings accord nicely with a previous report that cognitive function is better conserved in aged Nox2 knockout mice than in aged controls.[8]

Intriguing work by El Idrissi and colleagues has likewise provided suggestive evidence that age-related loss of GABAergic forebrain neurons contributes to age-related cognitive dysfunction in mice. Initial research established that short-term taurine supplementation (0.05% in drinking water for one month) in young mice markedly enhanced cortical levels of somatostatin-positive GABAergic cortical neurons.[9] This finding prompted a long-term study, in which mice were administered taurine from age 8 months to age 16 months; concurrently, a group of two-month –old mice were administered taurine for 4 weeks. In comparison to age-matched mice not supplemented with taurine, taurine supplementation did not influence learning and memory capacity in young mice, as assessed by a passive avoidance test; however, the taurine-supplemented 16 month-old mice showed a remarkably superior performance on this test as compared to control 16-month-old mice.[10, 11] The authors credibly speculated that taurine had exerted a trophic effect on the forebrain GABAergic neurons of aging mice, aiding their survival and/or function, such that cognitive decline was substantially blunted.

If indeed oxidant-driven loss of forebrain GABAergic neurons is a key mediator of age-related cognitive decline in mice, one would expect that a range of measures that provide effective antioxidant protection to the brain, if implemented continually beginning in mid-life, could ameliorate this cognitive decline, as Dugan's group reported for the compound C3. (The protection of GABAergic neurons mediated by taurine does not seem likely to reflect an antioxidant mechanism; modulation of intracellular calcium metabolism or agonism for GABA receptors are more credible options in this regard.[12]) Indeed, a search of the literature reveals that long-term administration of a range of antioxidants, including astaxanthin, N-acetylcysteine, lipoic acid, and melatonin, as well as spirulina, the green tea catechin EGCG, the spin-trapping antioxidant PBN, and various antioxidant-rich food extracts (which might aid neuronal antioxidant defense via phase 2 induction) has been reported to blunt age-related cognitive decline of either normal rodents or of senescence-accelerated mice.[13-21] Spirulina may be especially promising in this regard, as it is a rich source of the phytochemical phycocyanobilin (PhyCB), recently shown to mimic the ability of bilirubin to inhibit NADPH oxidase complexes;[22] this is of particular interest in light of Dugan's evidence that NADPH oxidase is likely to mediate the age-related die off of GABAergic

neurons.   Previous studies show that orally administered spirulina or phycocyanin (the spirulina protein which contains PhyCB as a chromophore) are protective in mice injected with kainic acid - an inducer of central excitotoxicity - or MPTP, which kills dopaminergic neurons in the substantia nigra; hence, orally administered PhyCB appears to have good access to the brain.[23, 24] A more recent rat study has found that dietary spirulina can counteract the adverse impact of intraperitoneally administered lipopolysaccharide on proliferation of stem/progenitor cells in the hippocampus.[25]

However, it seems unlikely that prevention of age-related die off of GABAergic neurons could explain the benefits seen in all of these studies, as in some instances the supplements were administered for only a modest portion of the lifespan. For example, a supplementation regimen of mixed antioxidants, in conjunction with a program of behavioral enrichment, employed for 1 year in dogs that were already up in years (9-12 years of age), was found to have a dramatically positive impact on cognitive performance;[21] it is hardly credible that a one-year slowing of GABAergic neuron death in dogs that were already elderly would have such a large impact.

Chronic Microglial Activation Likewise Promotes Cognitive Impairment in the Healthy Elderly

Indeed, there is a seemingly separate line of thought regarding the origins of age-related cognitive decline that has attracted much more attention than the GABAergic theory – the neuroinflammatory hypothesis.[26, 27] For reasons that remain to be clarified, aging is associated with a considerable increase in the number of brain microglia that are either in an activated, pro-inflammatory state, or that are primed for activation by systemic infection, trauma, or inflammation. This likely accounts for the fact that brain levels of certain cytokines produced by activated microglia, most notably interleukins 1 and 6, have often been found to be elevated in aging animals either constitutively, or for prolonged periods following infection.[26, 27] Interleukin-1 (IL-1) is of particular interest in this regard; although a certain basal level of IL-1 activity is required for effective cognitive function, high levels markedly compromise long-term potentiation (and hence cognitive function) in the hippocampus.[28, 29] The adverse impact of IL-1 in this regard appears to be mediated by an activation of neuronal stress-activated protein kinases that may be contingent on an increase in neuronal oxidative stress;[29-31] this pathway also is a mediator of the adverse effect of amyloid beta on long-term potentiation (LTP).[32] IL-1 appears to have little impact on the early phase of LTP, mediated acutely by calcium influx, whereas it notably impairs late-phase LTP, dependent on activation of CREB and production of brain-derived neurotrophic factor (BDNF), required for long-term memory formation.[27] In aged rats, infection suppresses hippocampal levels of mature BDNF, and this effect is prevented by injection of IL-1Ra (a cytokine antagonist of the IL-1 receptor) into the cisterna magna.[33]

In a recent study examining rats at 3, 9, and 15 months of age, hippocampal levels of IL-1 and of markers of microglial activation correlated inversely with the efficacy of hippocampal LTP.[26] In humans, studies suggest that certain haplotypes of the IL-1 gene thought to be associated with increased activity tend to correlate with poorer cognitive function in the non-demented elderly[34-36] – whereas cognitive function was found to be superior in elderly people homozygous for a reduced-activity allele of IL-1beta converting enzyme (required for production of mature IL-1beta); these findings evidently are consistent with the possibility that IL-1 of microglial origin plays a role in the age-related cognitive decline of humans. The antibiotic minocycline is known to suppress microglial activation; remarkably, in 15 month-old mice, administration of minocycline for just 7 days was found to have a markedly favorable impact on hippocampal LTP.[26]

A few regions of the adult brain, such as the dentate gyrus of the hippocampus, are capable of generating new neurons. Microglial inflammation can suppress this process, and there is reason to believe that this phenomenon contributes to brain aging.[37]

Measures Which Control Microglial Activation Ameliorate Age-Related Cognitive Decline

Quite a number of nutraceutical, pharmaceutical, and lifestyle measures have the potential to prevent or reverse activation of brain microglia, and it is not likely to be coincidental that many of them are also associated with increased LTP and improved cognitive function in animals. Spirulina, which is reported to aid preservation of cognitive function in senescence-accelerated mice (SAMP8),[17] has clear potential for controlling microglial neuroinflammation, as activation of NADPH oxidase is a central mediator of microglial activation; conversely, when NADPH oxidase activity is inhibited, LPS exposure tends to drive microglia to an IL-4-dependent "alternative" phenotype that is anti-inflammatory and neuroprotective.[38-41] In particular, NADPH oxidase inhibitors block the microglial production of IL-1 evoked by lipopolysaccharide (LPS) or interferon-γ.[38] Indeed, concurrent exposure of microglia to phycocyanin, the spirulina protein which carries PhyCB as a chromophore, suppresses LPS-mediated induction of iNOS, COX-2, TNFalpha, and IL-6.[42] Moreover, in rats, dietary spirulina offsets the adverse impact of systemic LPS administration on the proliferation of neural stem cells in the dentate gyrus – an effect likely attributable to dampening of microglial activation.[37] The premier membrane antioxidant astaxanthin, which may aid control of mitochondrially-derived oxidative stress, can also down-regulate LPS-mediated microglial activation. [43, 44]

The potential of dietary flavonoids for modulating microglial function has received considerable attention.[45] A number of groups have demonstrated that low micromolar concentrations of luteolin can suppress LPS-meditated microglial activation;[46-52] high dietary intakes of luteolin (for 4 weeks) also achieve this effect in vivo in aged mice, while improving their spatial working memory.[53] The structurally homologous flavonols fisetin and quercetin likewise can suppress LPS-mediated microglial activation, and parenteral administration of quercetin had a favorable impact on the cognitive function of aged mice and of mice injected with LPS, but not young mice.[53-56] These findings may be pertinent to a French prospective epidemiological study, which found that diets relatively rich in flavonoids were associated with lesser cognitive decline over a 10-year follow-up, after adjustment for age, sex, and educational level.[57] It should however be pointed out that most natural diets seem unlikely to achieve brain levels of flavonoids comparable to those which inhibit microglial activation in vitro; and confounding with other dietary factors might have played a role in the protection associated flavonoids in this study. In any case, a sufficient intake of certain flavonoids may have genuine potential for aiding cognitive function in the elderly.

Consumption of the catechin flavonoid epigallocatechingallate (EGCG) is particularly heavy in Japan, as this is the chief polyphenol in green tea. As little as 1 μM EGCG markedly blunts LPS-mediated induction of TNF-α in microglia.[58] (It is surprising that only one study to date has addressed this issue, as quite a number of studies have examined the impact of EGCG on amyloid beta metabolism.) A Japanese cross-sectional epidemiological study has found that heavy green tea consumption correlates with better cognitive function in the elderly; elderly subjects who habitually consumed 2 or more cups of green tea daily were only about half as likely as low consumers to score below 26 on the Mini-Mental State Examination.[59] Long-term consumption of green tea catechins had a favorable impact on hippocampus-

dependent cognitive function in aged rats and senescence-accelerated mice, and, in elderly subjects with mild cognitive impairment, 16 weeks of supplementation with a green tea catechin extract (which included a modest amount of theanine) was associated with better performance in certain tests of memory and attention.[60-62] Green tea catechins may be particular appropriate for nutraceutical regimens intended to preserve cognitive function in the elderly, as their potential to blunt neuroinflammation may be complemented by a favorable impact on risk for stroke, dementia, and fractures; in a recent prospective Japanese epidemiological analysis (Ohsaki Cohort 2006 Study), elderly subjects who at baseline were consuming 5 or more cups of green tea daily, as compared to those consuming minimal green tea, were about one-third less likely to experience onset of serious functional disability over 3 years of follow up as compared to low green tea consumers.[63]

Anthocyanins also appear to have important potential for cognitive preservation. Diets enriched in blueberries, which contain about 250 ppm anthocyanins per dry weight, have improved the cognitive performance of aging rats.[64, 65] Intact anthocyanins could be found in various regions of the brain after such feeding.[66] Although the impact of individual anthocyanins on microglia activation hasn't yet been assessed, at least in the published literature, ethanol or methanol extracts of the acai berry, especially rich in cyanidin glycosides, could suppress LPS-induced expression of iNOS or TNFalpha in microglia, in concentrations that corresponded to sub-micromolar concentrations of anthocyanins.[67] Analogously, anthocyanin-rich blueberry extract has been shown to inhibit LPS- or amyloid beta-mediated microglial activation *in vitro*, and blueberry feeding suppresses microglial activation in fetal hippocampal tissue grafted into aging rats.[68-70] Most intriguingly, 7 weeks of blueberry feeding increases spatial memory performance in *young* mice – an effect not credibly attributable to suppression of microglial activation, and similar to the impact of dietary fisetin.[71, 72] In the Nurses' Health Study, participants with the highest dietary intake of either blueberries or strawberries (a source of fisetin) were found to experience a delay in cognitive aging equivalent to about 2.5 years. [73]

Pterostilbene, a methoxylated derivative of the stilbene resveratrol, may also have potential for cognitive preservation. It is reported to inhibit LPS-induced activation of microglia and macrophages.[74, 75] Chronic feeding of low dietary levels of this agent was found to aid cognitive function in aging rats and in the SAMP8 mouse, a model of premature senescence associated with beta amyloid pathology.[76, 77] The pharmacokinetics of oral pterostilbene appear to be far superior to those of resveratrol, which may have little clinical potential.[78]

In vitro, the long-chain omega-3 fatty acid DHA blunts LPS- or interferon-γ-mediated cytokine production by microglia.[79-81] Dietary supplementation with omega-3 has benefited the cognitive function of aging rodents in some - but not all[82] - studies.[83, 84] Good omega-3 status has been associated with superior cognitive function in the elderly in several epidemiological studies;[85-87] a recent controlled clinical trial found that 900 mg of supplemental DHA for 24 weeks in cognitively-normal elderly subjects achieved significant improvements in several indices of cognitive function.[88] In contrast, fish oil appears to have little impact on cognitive function in patients with Alzheimer's disease.[85]

Vitamin D, via conversion to calcitriol in activated microglia, can provide feedback control of microglial activation.[89, 90] When aged rats were fed vitamin D3 in their drinking water for 2 weeks (0.1μg/ml – a dose that would be equivalent to 8,000 IU daily in a human drinking 2 liters per day), hippocampal levels of IL-1beta were found to be markedly lower than those in age-matched control rats. [91] These findings

are likely to be highly pertinent to emerging epidemiology correlating good vitamin D status with better cognitive function in the elderly.[92]

Lifestyle factors – exercise and dietary choices – can influence microglial activation. The benefits of exercise training for cognitive health, especially in the elderly, are well established, but not well understood; an increase in neurogenesis appears to be of key importance.[93-95] It is reasonable to suspect that suppression of neuroinflammation – which can suppress neurogenesis[96] - plays some role it its favorable impact on age-related cognitive decline. The most intriguing study to examine this compared sedentary aged rats with rats of comparable age allowed voluntary wheel running for 6 weeks.[97] After this training period, all rats received an intraperitoneal injection of LPS to provoke inflammation. 4 days thereafter, they received cognitive tests, and their brains were then removed for analysis. In the control rats, E. coli exposure caused marked microglial activation, associated with impaired hippocampus-dependent long-term memory, elevation of hippocampal IL-1beta mRNA and protein levels, and a reduction in BDNF mRNA. Remarkably, all of these effects were reversed by prior exercise training. In addition, microglia isolated from the hippocampi of exercised rats were less responsive to LPS activation than were microglia obtained from the sedentary rats. Another recent study examined the impact of exercise training on both adult and aged rats, and found that exercise increased the proportion of microglia that expressed IGF-I, and aided the survival of recently formed neurons.[98] Other recent research suggests that the favorable impact of exercise on neurogenesis may reflect, in part, a modulation of microglial phenotype that boosts the capacity of these cells to promote neuron growth and survival; this work also shows that exercise increases brain levels of CX3CL1, a chemokine that opposes microglial activation.[99]

A number of epidemiological studies suggest that diets with a low saturate/unsaturate ratio and/or rich in fruits and vegetables – a so-called "Mediterranean" dietary pattern" – are associated with lower risk for dementia and age-related cognitive decline.[100-110] Saturated fats, but not unsaturated fats, have the potential to activate both microglia and astrocytes via induction of oxidative stress and NF-kappaB activation; there is reason to suspect that de novo synthesis of ceramide from saturates may underlie this effect.[111-115] Saturate-rich diets are reported to have an adverse impact on the cognitive function of rodents, and this may be most detrimental in aged rodents.[116-118] In one of these studies, microglial activation was observed in the hippocampus of saturate-fed rats.[118] Another such study found that cortical NADPH oxidase expression and activity – likely primarily of glial origin – was elevated in rats fed a saturate-rich diet.[119] In mice, a diet high in saturates depressed hippocampal neurogenesis and levels of BDNF.[120] Arguably, the accelerated rate of cognitive decline often noted in metabolic syndrome, obesity and diabetes may reflect, in part, increased exposure of brain microglia to saturated fatty acids – albeit increased plasma levels of pro-inflammatory cytokines might also contribute to increased microglial activation in these disorders.[121-123]

The brain generates its own angiotensin II, which can boost microglial activation, at least in part by up-regulating microglial expression of NADPH oxidase.[124, 125] Indeed, LPS-stimulated microglia synthesize angiotensin II, and concurrent exposure to an angiotensin receptor antagonist lessens their state of activation.[125] Not surprisingly, brain-permeable angiotensin receptor antagonists can suppress brain inflammation in rodents.[125, 126] Lifelong treatment of several strains of rats with the brain permeable ACE inhibitor captopril was reported to ameliorate their age-related cognitive decline.[127] In the prospective Cardiovascular Health Study, elderly patients treated with brain-permeable ACE inhibitors were found to

experience considerably less cognitive decline in comparison to patients treated with brain-inpermeable ACE inhibitors or other drugs.[128] A recent overview of pertinent clinical trials concluded that, among available antihypertensive agents, brain-permeable ACE inhibitors and angiotensin receptor antagonists tended to be associated with the most positive cognitive outcomes.[129]

The AMPK-activating phytochemicals berberine and resveratrol have been found to suppress microglial activation in vitro.[130, 131] However, a study in mouse hippocampal slices has found that AMPK activation can impede the late phase of long-term potentiation via mTOR inhibition.[132] Although berberine has shown favorable effects on cognition in mouse models of Alzheimer's, it impact on the cognitive function of healthy aging rodents has not been studied.

The PDE5 inhibitors sildenafil and icariin also have the potential to suppress microglial activation; their efficacy in this regard likely reflects an increase in microglial levels of cGMP.[133, 134] cGMP can down-regulate microglial activation, and this may be a key homeostatic mechanism.[135, 136] Activated microglia make large amounts of nitric oxide via iNOS; the cGMP production which this provokes acts as a feedback signal to dampen activation. Icariin is of particular interest, as it is a key component of the traditional Chinese herb epimedium (a.k.a. horny goat weed!) that has access to the brain, and that has demonstrated neuroprotective properties in a number of rodent studies; in particular, long-term administration of icariin aids cognitive function in senescence-accelerated (SAMP8) mice.[137] Icariin also protects rats from the cognitive dysfunction induced by cerebral injection of LPS.[138] However, its clinical pharmacokinetics have received little if any study to date.

Age-Related Neuroinflammation and Loss of GABAergic Interneurons May Drive Each Other

Activated microglia also make cannabinoids, and these agents can provide feedback control of microglial activation via the CB2 receptors which are avidly expressed by microglia. However, the CB1 receptors expressed by hippocampal neurons – most prominently by GABAergic interneurons – may also play a key role in keeping microglial activation under control. In a particularly intriguing study, genetically modified mice were generated which GABAergic neurons selectively failed to express CB1 receptors.[139] At twelve months of age, mice of this strain had markedly impaired spatial learning capacity compared to age-matched control mice, and hippocampal neuroinflammation characterized by increased activated microglia, increased numbers of astrocytes, and elevated IL-6 levels was noted in these mice. To interpret these results, the authors hypothesized that GABAergic neurons "interpret" cannabinoid activity as a signal of microglial activation, and, as a homeostatic response, send out a still-to-be-characterized signal that dampens microglial activation, directly or perhaps indirectly. In the absence of CB1 receptors, the GABAergic neurons fail to receive the cannabinoid stimulus, and hence fail to provide the requisite feedback control of microglial activation. Hence neuroinflammation develops, and cognitive function suffers. This hypothesis comports well with the fact endocannabinoid production is about 20 times higher in microglia than in neurons or astrocytes, and that suppression of microglial activation with minocycline is associated with a marked reduction in 2-arachidonylglycerol production.[140, 141]

Of related interest is a recent study in which mesencephalic neurons were co-cultured with microglia.[142] Addition of the toxin MPTP to this co-culture led to the death of dopaminergic neurons, but only if the microglia were present. The addition of non-specific cannabinoids to this system protected the dopaminergic neurons and suppressed microglial activation, but this protection was eliminated by CB1 receptor antagonists. Neurons, but not microglia, express CB1 receptors, and this expression is

particularly high in GABAergic neurons, which play a key functional role in the substantia nigra. [143] These data therefore appear to be consistent with the hypothesis that CB1 agonists provoke GABAergic neurons to send a signal that opposes microglial activation.

The nature of the putative inhibitory signal which GABAergic neurons send to microglia remains undefined, but it is intriguing to note that a membrane glycoprotein expressed by neurons, CD200, as well as the chemokine CX3CL1, function to suppress microglial activation, and the levels of each tend to be decreased in the hippocampus of aging rats.[144-146] It would be interesting to know whether GABAergic interneurons are major sources of either of these and, if so, whether cannabinoid signaling enhances their expression. Ironically, GABA itself can suppress microglial activation[147] – but CB1 signaling has an inhibitory impact on GABA release![148]

This intriguing hypothesis now enables us to see how two of the leading theories of age-related cognitive decline may be functionally linked. As microglia become activated, the increased amounts of IL-6 they generate promote oxidative stress in GABAergic hippocampal neurons, resulting in their gradual death via excitotoxicity. In turn, the death of these neurons leads to loss of the putative signal which they provide that aids control of microglial activation – resulting in a yet higher level of microglial activation; the associated loss of GABA per se might also aid this activation. In other words, the loss of hippocampal GABAergic neurons and the activation of microglia that characterize "healthy" aging and mediate loss of cognitive capacity, may drive each other in an inexorable vicious cycle. It is not proposed that this is the *only* mechanism which leads to loss of GABAergic neurons or microglial activation with increasing age, but it is plausible that this mechanism could be of significant importance in this regard. An evident way to test this hypothesis would be to see whether measures which aid preservation of the GABAergic neurons (particularly taurine, which seems unlikely to directly impact microglial activity) tend to decrease microglial activation in aging animals. Conversely, measures which prevent microglial activation (notably minocycline or other strategies that are not overtly antioxidant) should tend to preserve GABAergic neurons during aging if this hypothesis has merit.

With respect to cannabinoids, despite the well known fact that acute high intakes have a transient adverse effect on memory formation, continuous intravenous infusion of a low dose of a non-specific cannabinoid receptor agonist, WIN-55212-2, for 21 days, was found to decrease the number of activated microglia in the hippocampi of 23-month-old rats while markedly improving their spatial learning abilities in the Morris water maze test.[149] In contrast, in 3-month-old rats, comparable infusion of the agonist provided no benefit for cognitive performance, and the lower of the two doses was associated with a significant reduction in performance; this presumably reflected the fact that microglial activation was of minimal significance in the young rats. It would be of practical interest to determine whether intermittent bolus doses of non-specific cannabinoid receptor agonists (including THC) could likewise blunt microglial activation in aged rats, and improve their cognitive function when cannabinoid levels were low. A positive finding in such a study might have intriguing implications for the cognitive function of elderly cannabis users.

Whether or not the hypothesis presented here proves to hold water, it is plausible to conclude that, if cognitive aging in humans is mechanistically comparable to that in rodents, nutraceutical, pharmaceutical, and lifestyle strategies capable of promoting the survival of hippocampal GABAergic neurons, and/or dampening the activation of microglia, may have genuine utility for improving the cognitive function of

aging humans. The greatest preservation of cognitive function would likely be seen in individuals who adopted such strategies in mid-life and used them continuously, as cognitive aging no doubt entails neuron losses and perhaps some phenotypic changes which are not readily reversible. But rodent studies suggest that strategies which quell microglial activation have the potential to boost cognitive function in the short-term. Hence, it may prove feasible to devise practical treatment protocols which can at least modestly improve the cognitive function of healthy elderly people.

Additional Mechanisms Promote Age-Related Cognitive Decline

With respect to agents which promote brain cholinergic function – effective choline supplements such as glycerophosphorylcholine, cholinesterase inhibitors such as donepezil and huperzine A, and possibly acetyl-L-carnitine[150-153] – and have aided cognitive function in some elderly individual with mild cognitive impairment, a recent study suggests that selective death of cholinergic neurons is *not* a feature of the neuroinflammation that characterizes healthy aging.[154] Hence, while these agents may be helpful in the early or interim stages of AD, it is not clear that they can benefit cognitive function in the healthy elderly. It will be difficult to bring more clarity to this issue until the earliest stages of AD can be more reliably diagnosed.

However, in regard to acetyl-L-carnitine, which has improved the cognitive function of elderly subjects in many clinical studies and in aging rats,[152, 153] there is credible speculation that this agent, alone or in conjunction with lipoic acid, may achieve this benefit in part by promoting mitochondrial biogenesis in neurons; the resulting improvement of mitochondrial structure and function might be expected to aid control of oxidative stress while optimizing ATP availability.[155-157] The mitochondrial theory of cognitive aging, while less well established at present than the neuroinflammatory and GABAergic theories highlighted here, merits further evaluation.[158] Clearly, the mechanisms of cognitive aging described in this essay are of cartoonish simplicity compared to the unimaginable complexity of the actual aging process.

In this regard, age-related loss of gray matter – reflecting primarily a loss of synaptic interconnections, rather than of cell bodies – seems likely to contribute to cognitive decline.[159] Although the inhibitory impact of neuroinflammatory hormonal activity on the late phase of LTP may play a role in this, it is unlikely to be the whole explanation. It would not be surprising if, independent of external factors, aging neurons tend to experience a loss of capacity for adaptive synapse formation. Wurtman and colleagues have demonstrated that supplementation for several weeks with dietary factors that can be rate-limiting for neural membrane formation – uridine, DHA, and bioavailable choline – can increase the formation of dendritic spines, neuritis, and synapses in adult rodents, while enhancing their cognitive function.[160-163] Would life-long implementation of such a strategy notably slow the age-related loss of gray matter? Of related interest are reports that exercise training can increase or preserve hippocampal and neocortical volumes in elderly humans, likely by boosting brain levels of neurotrophic hormones such as BDNF that support synaptogenesis and neurogenesis.[95, 164-167]

Suppression of Neuroinflammation May Also Slow Onset of Neurodegenerative Disorders

It should be noted that a number of the agents or strategies discussed above also have potential for prevention or control of common neurodegenerative conditions, such as Parkinson's disease or Alzheimer's.[168] There is considerable suggestive evidence, from rodent models, cell culture studies, and

human autopsy studies, that activated microglia are largely responsible for the death of dopaminergic neurons that characterizes Parkinson's disease.[169-172] Moreover, the clinical conditions suspected to trigger onset of Parkinson's have in common the ability to induce brain inflammation.[169] The substantia nigra may be particularly vulnerable to neuroinflammatory damage owing to its high content of both microglia and iron.[173] Hence, measures which dampen microglial activation may have real potential for preventing or managing this disorder. A number of the antioxidant measures discussed above have shown utility in the MPTP rodent model of Parkinson's, as have DHA, the AMPK activator resveratrol, cannabinoids, and brain-permeable antagonists of angiotensin II activity.[24, 174-183] It is reasonable to suspect that the relatively low incidence of Parkinson's noted in quasi-vegan societies or associated with a Mediterranean dietary pattern may reflect the up-regulatory impact of a high dietary saturate/unsaturate ratio on microglial activation; not surprisingly, saturate-rich diets exacerbate neuronal damage in rodent models of Parkinson's.[184-187] The lower risk for Parkinson's associated with mid-life exercise is also consistent with a role for microglia in the pathogenesis of this disorder.[188, 189]

Activated microglia also are observed in AD, reflecting at least in part the ability of amyloid beta to promote such activation, and there is considerable speculation that microglia may play a mediating role in the neuronal dysfunction, structural impairment, and death which characterize this disorder.[190-192] On the other hand, dystrophy and death of microglia have been observed in the latter stages of AD, and the phagocytic activity of microglia, particularly those that are blood-derived, can aid clearance of amyloid plaque and oligomers.[193] In transgenic mouse models of AD, the syndrome can proceed in the total absence of microglia;[194] clearly, microglia do not play as central role in the pathogenesis of AD as they do in Parkinson's. Nonetheless, cytokines and oxidants of microglial origin have the potential to promote or exacerbate AD.[192, 195, 196] In particular, IL-1 can boosting expression of beta-amyloid precursor protein, stimulate various tau kinases, and enhance acetylcholinesterase activity;[197-200] likely, its adverse impact on the late phase of long-term potentiation could be additive to the impact of amyloid beta in that regard. Concurrent injection of IL-1 receptor antagonist is reported to blunt the impact of amyloid beta injection on hippocampal LTP; cerebral injection of IL-1 receptor blocking antibody improves cognitive function and attenuates tau pathology in a transgenic mouse model of AD.[201, 202] Polymorphisms of the IL-1A and IL-1B genes associated with increased activity have been linked to increased risk for AD, or earlier onset of this disorder, in many though not all epidemiological analyses.[192, 203, 204] It is therefore credible to speculate that the microglially-mediated increase in brain IL-1 expression that accompanies aging may help to explain why AD most commonly manifests only at advanced age, and why certain disorders linked to chronic microglial activation, such as Down's syndrome, depression, and brain trauma, are also associated with increased AD risk.[192] If such speculation is correct, then measures which blunt age-related microglial activation may have potential for postponing or preventing AD.

It is reassuring to note that minocycline does not blunt the capacity of microglia to phagocytize amyloid beta; hence, the pro-inflammatory activation of microglia and microglial phagocytic capacity may not be tightly linked.[205, 206] Indeed, the capacity of microglia to phagocytize fibrillar amyloid beta is impaired by pro-inflammatory cytokines and by amyloid beta oligomers (possibly explaining why amyloid plaques persist in the aging hippocampus despite the presence of microglia); this effect is antagonized by measures which block NF-kappaB activation or control oxidative stress.[207, 208] Hence, many of the agents which impede microglial "activation" may also help to preserve microglial capacity for phagocytizing amyloid beta fibrils.

In transgenic mouse models of AD, or in senescence-accelerated mouse strains, in which hippocampal production of amyloid beta oligomers is increased, a number of the agents mentioned above have shown benefit; these include spirulina, melatonin, EGCG, sildenafil, icariin, pterostilbene, DHA, berberine, minocycline, and brain-permeable angiotensin antagonists.[17, 77, 209-220] Diets with a low saturate/unsaturate ratio (Mediterranean or vegan) and regular exercise also likely are protective with respect to AD risk.[101, 104, 221-223] The extent to which suppression of microglial activation contributes to these benefits is uncertain, as many of these agents can act directly on neurons, astrocytes, or the microvasculature. In any case, it may prove feasible to design nutraceutical/pharmaceutical/lifestyle regimens which not only aid preservation of cognitive function during healthy aging, but that in the process also help to ward off devastating neurodegenerative disorders.

Stroke Prevention is No Less Important

And some of the strategies cited above would also likely help to prevent stroke. Clearly, any comprehensive regimen intended to optimize preservation of cognitive function in the elderly must include elements that promote cerebrovascular health and minimize stroke risk. This huge topic cannot be addressed adequately here. Suffice it to say that exercise training, weight control, a diet high in potassium and moderate in sodium,[224] low-dose aspirin, vascular antioxidants (spirulina, high-dose folate),[225] flavonoids which support endothelial nitric oxide release (quercetin, and flavanols from cocoa or green tea),[226, 227] dietary nitrate,[228] and pharmaceutical control of hypertension, are either well documented to decrease stroke risk, or have credible potential in this regard. And yet to be explained are reports that traditional societies which minimally salt their food are at very low risk not only for hypertension and stroke, but AD as well.[229]

Few things are more delightful than encountering a very elderly individual who is energetic and "as sharp as a tack". Conversely, a not-to-be-forgotten U.S. Vice President was inadvertently wise when he remarked that "a mind is a terrible thing to lose." There is good reason to hope that, in the not-too-distant future, people with a prudent concern for their own wellbeing will have access to practical strategies that can greatly improve their chances of reaching a very advanced age with minimal loss of cognitive capacity.

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