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Down-regulation of microglial activation may represent a practical strategy for combating neurodegenerative disorders

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Summary Chronic neurodegenerative disorders are characterized by activation of microglia in the affected neural pathways. Peroxynitrite, prostanoids, and cytokines generated by these microglia can potentiate the excitotoxicity that contributes to neuronal death and dysfunction in these disorders — both by direct effects on neurons, and by impairing the capacity of astrocytes to sequester and metabolize glutamate. This suggests a vicious cycle in which the death of neurons leads to microglial activation, which in turn potentiates neuronal damage. If this model is correct, measures which down-regulate microglial activation may have a favorable effect on the induction and progression of neurodegenerative disease, independent of the particular trigger or target involved in a given disorder. Consistent with this possibility, the antibiotic minocycline, which inhibits microglial activation, shows broad utility in rodent models of neurodegeneration. Other agents which may have potential in this regard include PPARγ agonists, genistein, vitamin D, COX-2 inhibitors, statins (and possibly policosanol), caffeine, cannabinoids, and sesamin; some of these agents could also be expected to be directly protective to neurons threatened with excitotoxicity. To achieve optimal clinical outcomes, regimens which down-regulate microglial activation could be used in conjunction with complementary measures which address other aspects of excitotoxicity.

Chronic microglial activation as a mediator of neurodegeneration

There is growing evidence that activated microglia play a key pathogenic role in chronic neurodegenerative disorders as well as in the tissue damage consequent to stroke or brain trauma [1–8]. For reasons that remain largely obscure, the death or dysfunction of neurons typically results in activation of neighboring microglia. When activated, these microglia become a prominent source of oxidants, prostanoids, and inflammatory cytokines; this in turn can promote death and dysfunction of neurons, resulting in a vicious cycle in which a progressive loss of neurons is accompanied and abetted by sustained microglial activation.

The chief mediator of the pathogenic impact of activated microglia appears to be peroxynitrite [9]. This arises owing to activation of microglial NADPH oxidase — a potent generator of superoxide that in the brain is expressed primarily in microglia

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— in conjunction with induction of the inducible isoform of nitric oxide synthase (iNOS); the superoxide and nitric oxide (NO) produced by these enzymes can react avidly and spontaneously to yield the potent oxidant peroxynitrite, which readily diffuses through cell membranes, and thus can attack neighboring neurons and astrocytes. Superoxide per se does not readily penetrate cell membranes, and its product hydrogen peroxide is a relatively weak oxidant (except in the presence of free iron or copper). NO per se is only toxic at high concentrations. Thus, superoxide and NO are much more toxic jointly than separately, as they give rise to peroxynitrite. A central role for peroxynitrite in the pathogenicity of activated microglia is consistent with evidence that inhibition or diminished expression of either NAPDH oxidase or iNOS substantially reduces the neurotoxicity of activated microglia in vitro, and diminishes the severity of rodent neurodegenerative syndromes in vivo [10—20].

In neurodegenerative conditions, neuronal death, whether from necrosis or apoptosis, is typically associated with, and mediated by, excessive free intracellular calcium (induced by excitotoxic glutamate exposure), oxidant stress, and mitochondrial dysfunction (leading to ATP deficit and/or superoxide production) [21—25]. Glutamate-mediated excitotoxicity appears to play some role in most acute or chronic neurodegenerative conditions, and oxidant stress, as well as inefficient bioenergetics (owing to mitochondrial failure or ischemia, for example), can markedly potentiate the toxicity of glutamate to neurons [10,23,26]. In particular, peroxynitrite derived from microglia has been shown to boost cell death in glutamate-exposed neurons in vitro [10]. The basis of this effect is still unclear, although peroxynitrite attack on the mitochondrial respiratory chain — most notably complexes I and II [27—30] — as well as oxidant damage to membrane ion transporters [31,32], likely contribute. ATP deficit impairs the mechanisms which expel and sequester free intracellular calcium — thus exacerbating calcium overload — and can promote necrotic or apoptotic cell death by additional mechanisms. In vivo, microglial-derived peroxynitrite also promotes excitotoxicity by inhibiting the transport mechanisms by which astrocytes sequester extracellular glutamate [20,33,34]. Thus, peroxynitrite promotes excitotoxicity both by increasing the exposure of neurons to glutamate, and by increasing the sensitivity of neurons to this neurotransmitter.

It should be noted that activated microglia are not the only source of peroxynitrite in neurodegenerative conditions. The excess in intracellular free calcium associated with excitotoxicity strongly activates the neuronal isoform of nitric oxide synthase (nNOS), expressed in a high proportion of neurons [21,35]. Furthermore, nNOS is often partially ''uncoupled'', owing to suboptimal intracellular levels of arginine and/or tetrahydrobiopterin; this means that the calcium-activated enzyme produces superoxide as well as NO, enabling production of peroxynitrite within neurons [36—38]. Dysfunctional neural mitochondria can also act as a source of superoxide. This presumably explains why nNOS knockout mice tend to be less sensitive to ischemia or neurotoxins [35,39,40]. The implication is that suppression of microglial activation may only partially alleviate the pathogenic impact of peroxynitrite in neurodegenerative disorders.

The inducible form of cyclooxygenase (COX-2) is also induced in activated microglia [41,42]. COX-2-derived prostanoids are somewhat analogous to peroxynitrite in regard to their impact on excitotoxicity: they act directly on neurons to increase their susceptibility to glutamate-induced death, and they induce astrocytes to extrude rather than sequester glutamate [43—47]. Although COX-2 is minimally expressed in healthy neurons, it can be induced in neurons undergoing excitotoxicity [45]; the resulting increase in prostanoid production can have a feed-forward impact on glutamate toxicity.

Activated microglia also produce a range of inflammatory cytokines, including IL-1 and TNF-α. The latter has been reported to potentiate glutamate-mediated neurotoxicity — although a contrary finding has also been reported [48,49]. These cytokines can also suppress glutamate uptake and metabolism by astrocytes [50—53]. Thus, microglial-derived cytokines may contribute to excitotoxic neurodegeneration — although the evidence for this is less clear-cut than in the case of peroxynitrite or prostanoids.

The proportion of brain microglia which are activated tends to increase as a function of aging; this is observed even in animals and humans that have not been traumatized and who do not suffer from known neurodegenerative disease [54—56]. This phenomenon might help to explain why chronic neurodegenerative disorders are far more common in the elderly. Furthermore, microglial activation may become self-sustaining; activated microglia are observed in the substantia nigra of monkeys fully a year after a single administration of MTPT [57]. A similar phenomenon has been noted when humans transiently exposed to MTPT are autopsied [58]. It is not clear whether this prolonged activation might stem from autocrine mechanisms, or whether it is sustained by the continuing death

and dysfunction of neurons damaged by the activated microglia.

Activated microglia in Parkinson's and Alzheimer's diseases

In Parkinson's disease, microglial activation is prominent in the substantia nigra [21,4,59]. Dopaminergic neurons, high in iron and low in glutathione, appear to be unusually sensitive to oxidant stress [60]; moreover, the healthy substantia nigra is hosts a relatively high concentration of microglia. It thus is not surprising that a continuous intracerebral infusion of lipopolysaccharide (LPS) in rats, resulting in activation of microglia, leads to selective loss of dopaminergic neurons in the substantia nigra [61,62]; a similar effect has been reported following thrombin infusion [63]. This effect can be replicated in vitro — when dopaminergic neurons are co-cultured with microglia, addition of LPS leads to death of the neurons [18]. Microglial oxidant production appears to be a key mediator of this effect, since inhibitors of NADPH oxidase, or the use of microglia in which this enzyme complex is genetically defective, prevents neuron death. Analogously, the ability of rotenone or of MTPT to promote degeneration of dopaminergic neurons in vivo or in vitro is substantially suppressed when NADPH oxidase activity is concurrently inhibited or is genetically defective [14,15,17]. The inducible nitric oxide synthase (iNOS), prominently expressed in activated microglia, also appears to contribute to oxidant-mediated death of dopaminergic neurons, since pre-administration of iNOS inhibitors, or use of mice genetically deficient in this enzyme, protects rodents from MTPT- or LPS-induced parkinsonism [11,64,62]. These findings are clearly consistent with the possibility that microglia-derived peroxynitrite is a key pathogenic factor in Parkinson's disease.

With respect to Alzheimer's disease, microglial activation is likewise prominent in affected brain regions in this disorder [3,65], and it has been observed that β amyloid-42 is far more toxic to neurons in vitro when they are co-cultivated with microglia [13]. This toxicity is markedly blunted when the microglia used in this study are derived from NADPH oxidase-deficient mice — consistent with the fact that β amyloid strongly activates this enzyme in microglia [66]. Moreover, cytokines produced by activated microglia can both stimulate neuronal production of β amyloid precursor protein, and promote its conversion to β amyloid [67—69]; COX-2 products likewise up-regulate production of β amyloid [69,70]. This suggests a vicious cycle in which neural production of β amyloid leads to microglial activation, which in turn promotes neuronal cell death while further stimulating β amyloid production [3].

Broad efficacy of minocycline confirms a pathogenic role for microglia

The antibiotic minocycline, which readily penetrates the blood-brain barrier, has been shown to suppress microglial activation triggered by a broad range of activating stimuli; furthermore, it can do so in concentrations that are close to the clinical range for this well-tolerated drug [71—76]. The biochemical basis of this effect is not clear, although prevention of p38 MAP kinase activation appears to play a key role in this regard [71,74]; p38 signalling plays a central role in microglial activation [77]. Thus, it is of particular interest that pre-administration of minocycline has been shown to protect rodents from a wide range of neurodegenerative conditions, including rodent models of Parkinson's and Huntington's diseases, ALS, multiple sclerosis, stroke, excitotoxicity, and brain trauma [75,76]. These findings may be interpreted as strongly suggestive evidence that microglial activation is a prominent mediator of the neural death and dysfunction that characterizes these syndromes. Moreover, they have encouraged clinical efforts to evaluate minocycline as a neuroprotective agent in a range of disorders; for example, the impact of minocycline therapy on the progression of Parkinson's disease is currently being studied.

In addition to minocycline, a variety of other agents and strategies have the potential to down-regulate microglial activation, and thus possibly provide protection from a range of neurodegenerative disorders. Some of these are drug-related strategies — such as minocycline — that could most appropriately be applied in patients who are in the early stages of neurodegenerative disorders, or who are at very high genetic risk for same. Other strategies, involving nutrients and food factors, might reasonably be included in lifestyle regimens for healthy people who wish to preserve effective brain function to a ripe old age.

PPARγ agonists

Microglia express the PPARγ transcription factor, and agonists for this receptor, such as pioglitazone,

inhibit LPS-triggered induction of iNOS and of TNF-α in microglial cell culture [78—80]. Increased expression of IκB-α, which inhibits activation of the NF-kB transcription factor, may mediate this effect [81] — although contrary evidence has also appeared [78]. In vivo, pioglitazone pre-treatment protects dopaminergic neurons in the substantia nigra of mice treated with MPTP; it is somewhat less effective in preventing loss of dopaminergic terminals in the striatum [81,82]. Pioglitazone and other PPARγ agonists also have a favorable impact on the processing of β amyloid precursor protein, reducing the expression of the β-secretase required for production of β amyloid; they also diminish Alzheimer's-like pathology in transgenic mice which overexpress the β amyloid precursor protein [69,83,84]. Moreover, this drug is effective in experimental autoimmune encephalomyelitis, a rodent model of multiple sclerosis, and an anecdotal report of apparent response to this agent in an MS patient has appeared [85,86]. Given the fact that pioglitazone is a well tolerated drug, this agent merits further clinical evaluation in neurodegenerative syndromes.

PPARγ agonists may also have direct effects on certain neurons that protect against excitotoxicity. In cultured cerebellar granule neurons, administration of troglitazone up to 2 h following glutamate exposure was protective, even though the elevation of intracellular free calcium was not influenced; evidently, PPARγ influences a downstream event triggered by calcium overload [87].

Genistein

Parkinson's disease and ALS appear to be more common in men than in women; furthermore, epidemiological studies suggest that early menopause may increase risk for Parkinson's disease, whereas postmenopausal estrogen replacement may reduce this risk [88—91]. Thus, it is notable that estrogen exerts anti-inflammatory effects on microglia, acting via either isoform of the estrogen receptor [92,93]; this may rationalize the utility of estrogen therapy in rodent models of Parkinson's diseases [94—97]. With respect to Alzheimer's disease, epidemiology has pointed to a protective role for postmenopausal hormone replacement, whereas estrogen administration to elderly women in prospective studies has not shown such protection; the discrepancy between these results remains to be explained [98,99].

Although both isoforms of the estrogen receptor are expressed in the brain, the expression of ERβ is broader and more prominent; the brains of ERβ knock-out mice show marked abnormalities [100]. In light of the fact that hippocampal neurons are targeted in dementia, it is notable that ERβ is the predominant isoform in the primate hippocampus [101,102]. Microglia express ERβ, and selective agonists for this receptor exert anti-inflammatory effects on microglia, suppressing LPS-mediated induction of both iNOS and COX-2 [93]. Genistein, a potent and selective agonist for this receptor in physiologically achievable concentrations, is protective in rodent models of ALS and stroke [103]. Furthermore, in the low nanomolar free concentrations that can be achieved clinically, genistein alleviates the cytotoxicity of β amyloid to a neuroblastoma-derived cell line as well as cultured hippocampal neurons; this effect presumably reflected interaction with neuronal estrogen receptors, however [104,105]. Genistein likewise can alleviate the dopaminergic neurodegeneration evoked by LPS in rat mesencephalic-glia cultures; however, high nanomolar concentrations were required for this effect, suggesting that tyrosine kinase inhibition may have been responsible [106]. Further evaluation of genistein in rodent models of neurodegeneration appears warranted. Physiologically significant intakes of genistein have the potential to provide a range of protective health benefits, owing to the ability of this agent to activate ERβ at concentrations that have minimal impact on the cancer-promoting ERα receptor [107]. An oral daily intake of 54 mg genistein has demonstrated beneficial clinical effects in recent studies [108,109]; this would be supplied by about 150 mg of mixed isoflavone glycosides extracted from soy.

ERβ can also provide direct protection from excitotoxicity in some neural pathways. Thus, specific agonists for ERβ have been shown to induce the anti-apoptotic protein Bcl-2 in hippocampal neurons; these agents protect hippocampal neurons from glutamate-mediated excitotoxicity in vitro, and from brief global ischemia in vivo [110—113]. The protective impact of estrogen on MPTP-treated rats appears to be mediated by ERα receptors [97]; however, another study suggests that ERβ is responsible for the favorable influence of estrogens on cultured dopaminergic neurons exposed to MPP(+) [114].

Vitamin D

Microglial cells express the vitamin D receptor, and calcitriol inhibits expression of iNOS by microglial cells exposed to LPS and other activating agonists

[115—117]. This may reflect the presence of a vitamin D response element in the promoter of the iNOS gene. Furthermore, calcitriol boosts astrocyte production of glial-derived neurotrophic factor (GDNF), a growth factor that provides particular protection for dopaminergic neurons of the substantia nigra [118,119]. In rats, calcitriol administration has a protective effect in 6-hydroxydopamine-induced Parkinsonism as well as in experimental autoimmune encephalomyelitis [120,121].

1α-Hydroxylase, the enzyme which converts 25-hydroxyvitamin D to the active hormone calcitriol, is expressed by activated but not quiescent microglia [122]. Thus, activated microglia generate calcitriol when incubated with 25-hydroxyvitamin D. This raises the intriguing possibility that autocrine production of calcitriol by microglia could be boosted by improving vitamin D status; supplemental or autogenous vitamin D might have the potential to increase microglial and astrocyte exposure to calcitriol during the early stages of neurodegenerative syndromes — without entailing the hypercalcemic risk evoked by direct calcitriol administration. In this regard, incidences of both Parkinson's disease and ALS have been found to correlate positively with latitude [123—125]; no such relationship has been reported for Alzheimer's disease, however. High but tolerable doses of vitamin D — rather than calcitriol — should be studied in various rodent models of neurodegenerative disease. In humans, daily doses as high as 10,000 IU could reasonably be tested, inasmuch as physiological capacity for *uv*-catalyzed endogenous production of vitamin D is on the order of 10—20,000 IU daily [126].

COX-2 inhibitors

Individuals who have used NSAIDs chronically for years appear to be at substantially lower risk for both Parkinson's disease and Alzheimer's; this pertains to aspirin as well, but only when used in high anti-inflammatory doses [127,128]. This suggests that prostanoids derived primarily from COX-2 in activated microglia may act as mediators of neurodegeneration; indeed, as noted above, COX-2 products can sensitize neurons to excitotoxicity, while also impairing the ability of astrocytes to sequester glutamate [43—47]. The possibility that these prostanoids also act, directly or indirectly, to sustain microglial activation, is suggested by the observation that activated microglia are less common in the brains of humans or rodents that have been treated chronically with NSAIDS [55]. In vitro, COX inhibitors suppress expression of iNOS in LPS-activated microglia; perplexingly, PGE2 boosts this expression [129]. Supernatants derived from an microglial-like cell line (THP-1) activated with LPS are cytotoxic to neuroblastoma-derived cells in vitro; this cytotoxicity is largely alleviated if the THP-1 cells are incubated with COX inhibitors [130]. COX-2 inhibitors are protective in the MTPT model of Parkinsonism in mice, as well as in rodent models of Alzheimer's and ALS [131—133]. Although the increased cardiovascular risk associated with COX-2 inhibitor therapy has recently discouraged the use of these drugs [134], it seems likely that they would be no more risky than non-specific COX inhibitors if used in conjunction with low-dose aspirin to stabilize platelets. (Indeed, they might be safer, since the COX-1 activity of vascular endothelium would be largely preserved.) Thus, the use of COX-2 inhibitors + low-dose aspirin should be considered as a clinical neuroprotective strategy.

Diets high in fish and fish oil have been associated epidemiologically with decreased risk for Alzheimer's disease [135—137]. Could this reflect modulation by ω-3 fats of COX-2-mediated prostanoid production? Whether fish intake might influence risk for Parkinson's disease appears to have received little attention.

Statins — and policosanol?

Several — though not all [138,139] — case-control studies have concluded that patients who use statins may be at decreased risk for Alzheimer's disease [140—143]. These findings are subject to the bias that people who seek out and use medical care may tend to be more mentally competent than those who do not; however, one study noted that use of other types of lipid-lowering agents was not associated with protection in this regard [141]. Nor is high cholesterol per se protective — quite to the contrary, elevated LDL cholesterol may be a risk factor for dementia [144—147]. The impact of statin use on Parkinson's risk has apparently received little attention, although one study failed to note any evident impact of on-going statin therapy on the clinical course of the disease [148].

Evidence that statin therapy might reduce Alzheimer's risk has motivated several groups of researchers to examine the impact of statins on microglial activation. In vitro, statins suppress the rac1-dependent activation of NADPH oxidase and induction of iNOS in β amyloid-stimulated microglia [149]; LPS-mediated induction of iNOS

and of cytokines is also inhibited, as is secretion of apoE (which promotes β amyloid fibrillogenesis and deposition) [150,151]. These effects appear to be mediated by decreased isoprenylation of microglial signaling proteins, as they can be reversed by addition of geranylgeranyl pyrophosphate. There is, however, one discordant report, observing that statins themselves can have an activating impact on microglia [152]. There is also some evidence that statins may also have a favorable influence on the processing of amyloid precursor protein, such that β amyloid secretion is suppressed [153—155]; this effect may be mediated, in part, by reduced cellular cholesterol levels. Moreover, there are two reports that atorvastatin diminishes glutamate-mediated excitotoxicity in cortical neuron cultures [156,157]. Whether such effects can be achieved in vivo with tolerable clinical doses of statins, is not yet clear. Statins may vary with respect to their access to the brain; atorvastatin does not cross the blood-brain barrier [158]. Statins can also influence brain function by up-regulating endothelial expression of eNOS — an effect that could help to maintain efficient brain perfusion and thereby aid brain bioenergetics [159—161]. Statin pre-treatment decreases infarct volume following focal ischemia in rodents [162].

If statins do indeed have neuroprotective potential, it will be important to determine whether policosanol — a mixture of non-toxic sugar cane waxes which lowers LDL cholesterol by down-regulating expression of HMG-CoA reductase — likewise can be protective in this regard [163—165]. Whether policosanol can influence expression of this enzyme in the brain has not been determined. It is encouraging to note, however, that policosanol appears to share the osteoprotective properties of statins [166]; thus, its physiological effects may be parallel to those of statins. Moreover, hexacosanol acid, a component of policosanol, is reported to protect rats from central kainic acid-mediated excitotoxicity after intraperitoneal administration [167]. The particular merit of policosanol is that, whereas excessive concentrations of statins can induce severe toxicity by over-inhibiting HMG-CoA reductase in skeletal muscle, even very high concentrations of policosanol do not appear to reduce expression of this enzyme by more than about 50% [163]; this likely accounts for the non-toxicity of this agent in animal studies, and its excellent tolerability in clinical trials [168]. Thus, if policosanol proves to have neuroprotective activity, it would be feasible for the healthy general population to use this agent — without the regular physician monitoring that statin use entails.

Caffeine

Regular coffee drinkers are at markedly lower risk for Parkinson's disease [169], and two epidemiological studies suggest that Alzheimer's disease may also be less common in coffee drinkers [170,171]. Caffeine has well documented neuroprotective effects in a range of rodent models, including those for Parkinson's disease, stroke, and excitotoxicity [172]; moreover, caffeine is reported to decrease the toxicity of β amyloid to cultured cerebellar neurons in vitro [173]. This protection appears to reflect inhibition of adenosine type 2A receptors (A2A), widely expressed in the brain [172]. In particular, such receptors are found on microglial cells, and selective agonists for this receptor promote induction of COX-2 in these cells [174]. Thus, it is conceivable that caffeine neuroprotection reflects, at least in part, down-regulation of COX-2 expression in microglia. However, the main impact of A2A antagonists on neurodegeneration may reflect a down-regulation of glutamate release from excitatory synapses; evidently, adenosine plays a physiological role in promoting the extracellular glutamate excess that mediates excitotoxicity [175—178].

Importantly, whereas cardiovascular responses to caffeine tend to rapidly down-regulate, the protection afforded by caffeine in MTPT-induced Parkinsonism was seen in rats that had been chronically pre-treated with caffeine [179]. In light of the fact that the impact of caffeine on cardiovascular risk is equivocal, and heavy coffee use has been linked to reduced risk for diabetes, those who enjoy their daily coffee can take comfort in the thought that they may be protecting their brain in the process.

Cannabinoids

Cannabinoids, acting via CB1 or CB2 receptors expressed by microglial cells, inhibit LPS-mediated induction of iNOS in microglia [180,181]; they also inhibit activation of microglia by β amyloid, in vitro and in vivo, and prevent the cognitive dysfunction and neuronal death induced by intracerebral β amyloid administration in rats [182]. In addition, cannabinoids directly protect neurons from glutamate-mediated excitoxicity, in vitro and in vivo [181,183—188]; moreover, like A2A antagonists, they act on excitatory pre-synaptic terminals to suppress glutamate release [189—191]. It is suspected that glutamate acts post-

synaptically to trigger production of anandamide and other endogenous cannabinoid receptor agonists, which in turn act as a feedback signals to diminish pre-synaptic glutamate release. Cannabinoids and A2A antagonists both act presynaptically to decrease cAMP levels; cAMP up-regulates release of glutamate from glutaminergic terminals [192–195]. The fact that CB1 knock-out mice are more susceptible to excitotoxicity [188] suggests that anandamide feedback is of physiological importance (and moreover raises some concern regarding the possible impact of longterm use of rimonabant — the CB1-antagonist appetite suppressant — on risk for neurodegenerative disorders). Cannabinoids protect PC12 pheochromocytoma cells from β amyloid toxicity, are protective in a transgenic mouse model of ALS, and limit infarct volume in focal cerebral ischemia [196–198]. However, in a rat model for Huntington's disease (striatal malonate injection), tetrahydrocannabinol had an adverse effects, possibly because of its agonist activity for CB2 receptors [199].

The fact that microglia can express CB2 receptors suggests that selective CB2 agonists — which are not psychoactive — could have some neuroprotective activity. However, the cannabinoid receptors expressed on neurons are exclusively CB1 — so selective CB2 agonists could not be expected to provide the same level of protection as would nonselective agonists such as tetrahydrocannabinol.

Synthetic cannabinoids are now being assessed clinically in traumatic brain injury and stroke. Centrally-acting cannabinoids should be evaluated in a wider range of rodent models of neurodegeneration. There does not yet appear to be any epidemiology focusing on risk for neurodegenerative disorders in habitual cannabis users; perhaps Jamaica would be an appropriate venue for such research. As a caution, it should be noted that marijuana use by young people has been linked to increase risk for schizophrenia [200].

Sesamin

Various antioxidant phytonutrients, such as resveratrol, silymarin, and EGCG, have been shown to have a down-regulatory impact on microglial activation in vitro, presumably because these agents can inhibit NF-κB activation [201–204]. However, these effects require micromolar concentrations which would likely be impossible to sustain in vivo, owing to rapid metabolism of these agents. On the other hand, the intriguing lignan sesamin, a prominent component of sesame seeds, not only inhibits the LPS-mediated activation of microglial cells in vitro [205,206], but also protects against rotenone-induced Parkinsonism when fed to rats [207]. This may reflect the fact that sesamin, lacking hydroxyl groups, is less readily susceptible to conjugation in the liver, and thus can achieve ample concentrations in the serum and the brain. Although this phytonutrient is not yet widely available as a supplement, it might have considerable potential for neuroprotection, and should be evaluated further.

Complementary strategies

Suppression of microglial activation, by dampening excessive production of peroxynitrite and COX-2-derived prostanoids, can be expected to favorably impact the many neurodegenerative conditions in which excitotoxicity plays a prominent pathogenic role. However, there clearly are a number of additional strategies which might help to quell excitotoxicity — some of which would presumably be compatible with, and complementary to, microglial down-regulation.

Improve astrocyte performance

Astrocytes protect neurons by sequestering extracellular glutamate, converting it to glutamine; the adverse impacts of peroxynitrite and of COX-2-derived prostanoids on this mechanism have been cited. Astrocytes also produce a range of neurotrophic factors which function to protect neurons from apoptosis and which can support the production of new neurons when appropriate [208–210]. As we have noted, calcitriol can increase astrocyte production of several neurotrophic factors: nerve growth factor, neurotropin-3, and glial-derived growth factor. In rodents, caloric restriction, physical exercise, and environmental enrichment increase the expression of BDNF and of GDNF in various regions of the brain, including the cortex, hippocampus, and striatum [211–215]. The clinical correlate of this may be the reduced risk for Alzheimer's disease noted in those who engage in regular physical or mental exercise, or who consume relatively few calories [216–219]. Exercise training and lower-fat, lower-calorie diets also appear to be protective with respect to Parkinson's disease [220–223]. Mattson refers to caloric restriction, physical exercise, and mental activity as a type of ''hormesis'' — small stresses to the brain that up-regulate various

neuroprotective mechanisms which can help neurons to survive when faced with the larger stresses that trigger and sustain neurodegenerative disorders [211]. Other research is attempting to discover drugs which can act directly on astrocytes to promote production of neurotrophic factors; agents showing promise in this regard include various dopamine agonists, the anti-excitotoxic agent riluzole, the vasodilator ifenprodil, and the cognitive enhancer FK960 [224–228].

Down-regulate presynaptic glutamate release

This mechanism may be crucial to the neuroprotective activity of cannabinoids and of A2A receptor inhibitors such as caffeine. Maintaining good neuron bioenergetics is also of importance in this regard; during strokes, neuron depolarization consequent to ischemia promotes glutamate release, triggering excitotoxicity. Thus, preserving efficient cerebral circulation (for example, with high-potassium, low-salt diets and hypertension control) should be of value in this regard, as should supplemental nutrients which support neuron bioenergetics (see below).

Inhibit activation of NMDA receptors

Activated NMDA receptors are primarily responsible for excessive calcium influx during excitotoxicity. Unfortunately, most agents which directly inhibit NMDA receptors are unacceptably toxic, as they impair the long-term potentiation mechanism required for learning [229]. However, the drug memantine, long approved in Germany for the treatment of Alzheimer's disease, is a non-competitive NMDA receptor antagonist that has an intriguingly selective impact on these receptors – inhibiting the low-grade chronic activation of these receptors that is usually involved in excitotoxicity, while having relatively little impact on the sharp discrete signals required for long-term potentiation [230–232]. Thus, clinical tolerance to memantine is far superior to that for other NMDA antagonists. Memantine is effective in a range of rodent models of excitotoxicity, and is of documented clinical efficacy in Alzheimer's disease. Studies are underway to evaluate its utility in a wider range of neurodegenerative disorders. Another relatively well tolerated NMDA antagonist, the cough-suppressant dextromethorphan, may also have clinical potential as an anti-excitotoxic agent – albeit it did not improve survival in ALS in a recent clinical trial [233].

Activate postsynaptic GABA(A) receptors

These receptors, expressed on many postsynaptic dendrites, act to hyperpolarize postsynaptic membranes by boosting chloride conductance. This in turn impedes calcium influx via activated NMDA receptors. During excitotoxic episodes, neurons release taurine and GABA into the extracellular space, where they can activate postsynaptic GABA(A) receptors, providing feedback suppression of excitotoxicity [234–238]. Since taurine supplementation can boost brain taurine stores – by about 50% in rats [239] – it seems likely that such supplementation could help to control excitotoxicity. While there is clear evidence that taurine can suppress excitotoxicity in vitro [237,240–242] – for example, inhibiting β amyloid-induced death in cultured chick retinal neurons [242] – the impact of supplemental taurine on ischemia-induced neuronal death in vivo is more equivocal. Thus, whereas taurine preadministration has shown efficacy in some models of excitotoxicity [243,244], intracranial administration of taurine produced only modest non-significant protection in rat models of focal or global ischemia [245]. The extracellular taurine concentration measured in rat brains during ischemic episodes rises to the range of 5–18 μM [234,235] – whereas the affinity of taurine for the GABA(A) receptor is said to be 40–50 μM [238]. Thus, it is conceivable that the rise in extracellular taurine during excitotoxicity is of real, if perhaps modest, physiological significance as a feedback protective mechanism – in which case supplemental taurine would likely potentiate this neuroprotection. Taurine is reported to have modest and inconsistent efficacy for controlling epilepsy in children [246,247]; presumably, this could reflect a down-regulatory impact on glutamate transmission. Taurine also acts as a scavenger for the potent oxidant hypochlorous acid, which can be produced by activated microglia and possibly contributes to neurodegeneration [248]; moreover, taurine's natural derivative taurine chloramine can inhibit induction of iNOS in microglia [249].

The herb kava–kava, long used as a mild intoxicant by various South Pacific cultures, is a source of ''kavapyrones'' that appear to mediate its clinical activity in anxiety syndromes. These agents have been reported to induce a rapid up-regulation of GABA(A) receptor expression in the hippocampus and frontal cortex of rats [250]; however, they have no direct agonist activity for these receptors – possibly explaining why kava is better tolerated

and less habit-forming than direct agonists for these receptors such as benzodiazepines. The possibility that kava-kava may have neuroprotective activity is supported by a rat study demonstrating that kava extracts are approximately as effective as memantine in decreasing infarct volume following occlusion of the left middle cerebral artery [251]. Kava's utility in this regard — like that of memantine — may be more general, and it would be of interest to test it in the context of concurrent taurine supplementation.

Boost neuronal protective mechanisms

Neurons express a range of proteins — antioxidant enzymes, heat shock proteins, calcium sequestrants, anti-apoptotic factors — which can protect them from the potentially lethal consequences of calcium overload. It may be feasible to up-regulate the expression of these protective proteins. In particular, the broad spectrum neuroprotective utility of caloric restriction or intermittent fasting in rodents and monkeys, may largely reflect increased neuronal expression of a range of protective proteins — as well as a decrease in expression of pro-apoptotic glucocorticoid receptors [211,252,253]. Some, but probably not all, of this effect is secondary to increase production of neurotrophic factors, which function to promote neuron survival. Regular exercise and mental stimulation also have some efficacy in this regard [211]. The antioxidant capacity of neurons can also be boosted with the nutrient lipoic acid; in sufficient concentrations, this acts as a phase II inducer, increasing neuronal synthesis of glutathione while also increasing the expression of various antioxidant enzymes [254—256]. Presumably, this explains the versatile neuroprotective activity of lipoic acid in rodents [257—263]. Lipoic acid is a well tolerated nutrient — though the oral doses required for optimal efficacy (600—1800 mg daily have shown some clinical efficacy in diabetic neuropathy) [264] can be expensive. Maintaining adequate selenium status — of potential importance in regions of the world where soil selenium is low — should also support the antioxidant defenses of neurons [265—268]. Although the impact of α-tocopherol on neurodegenerative disorders is receiving attention — in light of evidence that lipid peroxides are mediators of the adverse impact of oxidative stress on neural function [32] — it would also be of interest to evaluate γ-tocopherol in this regard, inasmuch as this agent has a peroxynitrite-scavenging activity not possessed by α-tocopherol [269,270].

Support neuronal bioenergetics

Creatine acts as a ''energy buffer'' in excitable tissues that have rapidly varying energy requirements — such as muscles and neurons. Beal and colleagues have shown that supplemental creatine — which can boost brain stores of this nutrient — has versatile neuroprotective activity [271—274]. Other nutrients which appear to aid neuron bioenergetics under certain circumstances include coenzyme Q10 and acetylcarnitine [275—278]; a small clinical study has concluded that, at a dose of 1200 mg daily, coenzyme Q10 can slow clinical deterioration in Parkinson's disease [276]. Ketone bodies, which serve as alternative fuel for the CNS during fasting metabolism, can improve the bioenergetics of neurons when pyruvate dehydrogenase is suboptimally active; presumably, this is why ketotic diets are useful in the management of pediatric epilepsy, and why ketone infusion is protective in MPTP-induced neuropathy [279—281]. These findings point to the possible utility of medium-chain triglycerides (converted to ketone bodies in the liver) in the prevention and management of neurodegenerative syndromes [282].

Efficient cerebrovascular perfusion is evidently a *sine qua non* for optimal neuronal bioenergetics. Small strokes and diminished vascular perfusion are suspected to play a co-factor role in the induction of Alzheimer's dementia [283]. A low-salt, potassium-rich whole foods diet — the type of diet that humans evolved with — is associated with a low risk for hypertension and an even lower risk for stroke. On the Melanesian island of Kitava, whose inhabitants still do not salt their food, potassium intakes (primarily from yams) are as high as 8 g daily, the diet is quasi-vegan (small amounts of fish are consumed), and most people remain lean and insulin sensitive throughout life. Stroke appears to be rare or nonexistent among these people — many of whom live to an advanced age - and the very concept of senile dementia is unknown [284—286]. A similar rarity of senile dementia was reported among black East Africans during the early twentieth century, when salt use, hypertension, and stroke were still rare [286,287]. This suggests that preserving efficient cerebrovascular perfusion into old age may have a remarkably favorable impact on risk for dementia — not only vascular dementia, but also Alzheimer's. In Western epidemiology, obesity and hyperinsulinemia [288,289] — which may increase brain production of β amyloid [290] — have been linked to increased Alzheimer's risk, so the leanness of the Kitavans may contribute to their freedom from dementia;

nonetheless, stroke has been common in lean East Asian societies which heavily salt their food.

Promote proper coupling of nNOS

When neuronal levels of either arginine or tetrahydrobiopterin are suboptimal, activation of nNOS by excitotoxic calcium influx induces production of superoxide as well as of NO — giving rise to peroxynitrite [36,37]. Grima and colleagues have shown that arginine can protect neurons from glutamate toxicitiy in vitro [38]. Furthermore, they note that glutamate stimulates astrocytes to transfer arginine to neurons — a physiological mechanism that may aid control of excitotoxicity in vivo. Surprisingly, aside from a single study demonstrating that arginine pre-loading decreases infarct volume after simulated stroke (the benefit being attributed to improved cerebral perfusion) [291], there seem to have been few if any attempts to evaluate the impact of supplemental arginine on excitotoxic syndromes in rodents. Furthermore, little if any attention has been devoted to the possibility that tetrahydrobiopterin — readily oxidized by peroxynitrite [292] — might be suboptimally available in neurons threatened with excitotoxicity [37]. In this regard, it is intriguing to note that 5-methyltetrahydrofolate somehow compensates for tetrahydrobiopterin deficiency in endothelial cells, thereby accounting for the beneficial impact of high-dose folate on dysfunctional endothelium (independent of its impact on homocysteine levels) [293—296]. Could high-dose folate likewise have favorable impact on nNOS activity when tetrahydrobiopterin availability is limiting? Supplemental folate is already recommended for neuroprotection, inasmuch as elevated homocysteine has been found to be a risk factor for Alzheimer's disease and stroke [297,298]; however, the doses required to promote tetrahydrobiopterin function are higher than those required for homocysteine control.

Employ a range of complementary strategies

In the future, it seems likely that effective neuroprotection will be achieved, not by some single ''magic bullet'' drug, but rather by a mélange of well tolerated agents and lifestyle measures that address complementary aspects of the neurodegenerative process. As a demonstration of this principle, Beal and colleagues have recently shown that joint administration of creatine and a COX-2 inhibitor is much more effective than either agent alone in stemming loss of dopaminergic neurons in the MTPT model of Parkinsonism, and in preserving motor neurons in a transgenic mouse model of ALS [299,300].

Although neurodegenerative disorders share certain common features — microglial activation associated with excitotoxic neuronal death and dysfunction — they differ in the ''trigger'' mechanisms that target neurodegeneration to specific neural pathways. (For example, β amyloid overproduction in Alzheimer's, mutant superoxide dismutase in some cases of hereditary ALS). Thus, effective management or prevention of a specific neurodegenerative disorder may require measures which address the trigger specific to that disorder. Measures which provide symptomatic support by compensating for the neuronal losses characteristic of that disorder (e.g. l-DOPA in Parkinsonism, acetylcholinesterase inhibitors in Alzheimer's) will also continue to play an important role in therapeutic protocols.

What we can do now

Healthy people desiring to minimize their risk for neurodegenerative disorders could reasonably include the following in their daily supplement regimens (finances permitting!): vitamin D, soy isoflavones, creatine, selenium, coenzyme Q10, acetylcarnitine, lipoic acid, and taurine. Ingesting several strong cups of coffee daily (or taking a caffeine supplement) can also be recommended in this regard, along with regular physical and mental exercise, and moderation in calorie intake. For stroke prevention, frequent ingestion of potassium-rich whole foods, coupled with moderation in salt intake, is particularly advisable.

Presumably, it will be several more years before clinical trials enable us to judge the true merits of minocycline, pioglitazone, memantine, statins (or policosanol) and COX-2 inhibitors as clinical neuroprotective agents. However, since these drugs are usually well tolerated and reasonably safe (assuming that mini-dose aspirin is taken in conjunction with COX-2 inhibitors, and statin use is monitored), it may not be imprudent for patients in the early stages of neurogenerative disorders to use these drugs, providing that they can find a cooperative physician. They might also be well advised to avail themselves of the nutrients and lifestyle measures cited in the preceding paragraph.

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