Memo: Arian Foster's Whole-Food Vegan Diet May Protect Him from Trauma-Triggered Neurodegenerative Disorders

Summary: *Vegan and Mediterranean diets in which unsaturated fatty acids predominate may reduce the risk for neurodegenerative disorders associated with repeated brain injury by decreasing ceramide synthesis in microglia and astrocytes, and thereby suppressing the chronic neuroinflammation that drives neurodegeneration.*

Recently, the decision of star football running back Arian Foster to adopt a vegan diet, composed primarily of whole foods, has attracted considerable commentary. Many of these comments have been critical, rooted in the dubious notion that such a diet is incompatible with athletic excellence, or viewing this decision as an implied denigration of "the American way of life". Doubtless, Foster has been motivated largely by concern for his long-term health. While there is compelling reason to suspect that a whole-food vegan diet provides protection from common disorders such as coronary disease, diabetes, and cancer, I further propose that such a diet may mitigate to some degree the increased risk for neurodegenerative disorders associated with repeated head trauma, which has emerged recently as a issue of key concern for professional football players.

A recent epidemiological study has concluded that retired professional football players are at about threefold higher risk for death from neurodegenerative disorders than the general population; mortality from Alzheimer's disease (AD) and amyotrophic sclerosis (ALS) was found to be about fourfold higher.[1] Neurodegenerative mortality was significantly higher in speed players as opposed to linemen. These findings accord well with those of a previous analysis, in which retired football players who had suffered multiple concussions were at greater risk for mild cognitive impairment, and tended to develop Alzheimer's at an earlier age than controls.[2] Other studies have linked multiple mild traumatic brain injuries, as experienced by boxers, to increased risk for a distinct neurodegenerative syndrome known as chronic traumatic encephalopathy, and have observed increased risk for dementia in people who have suffered severe brain trauma.[3-5]

Giunta and colleagues have recently marshaled evidence pointing to chronic neuroinflammation, triggered by single or multiple episodes of brain trauma, as the likely driving force behind the subsequent development of neurodegenerative illness.[6] Activation of microglia to a pro-inflammatory phenotype, associated with production of inflammatory cytokines, peroxynitrite, and prostanoids, and characterized by increased antigen-presenting activity, is observed after brain injury, and often persists chronically thereafter.[7, 8] In a recent study, PET scans documented microglial activation in multiple brain regions persisting for a number of months after a single episode of brain trauma.[9] Pro-inflammatory microglia, as well as reactive astrocytes, are strongly suspected to play a pathogenic role in the evolution of AD, Parkinson's disease (PD), and a range of other neurodegenerative disorders.[10-17] Hence, lifestyle or pharmaceutical measures which modulate brain neuroinflammation may have important potential for influencing risk for neurodegeneration.

Plant-based diets, if not laced with tropical oils, tend to be low in saturated fatty acids, both absolutely and relative to total fat content. So-called "Mediterranean diets", low in red meats and fatty dairy products, are also associated with a low ratio of saturated to unsaturated fat. Considerable epidemiology, much of it prospective, has linked adherence to a Mediterranean diet pattern to decreased risk for mild cognitive impairment, AD, and PD.[18-29] There is accumulating evidence that the saturated fats palmitate and stearate can promote neuroinflammation via direct effects on microglia and astrocytes; this stems, at least in part, from the fact that these fats are uniquely capable of supporting the synthesis of the signaling intermediate ceramide. Palmitate and stearate are obligate substrates for serine palmitoyltransferase, the rate-limiting enzyme for *de novo* ceramide synthesis.[30] Both the absolute dietary intake of these fats, and the fraction of total dietary fat content that they constitute, can be expected to modulate blood and tissue levels of these fats, and hence influence the efficiency of ceramide synthesis. Dietary modulation of tissue fatty acid profile should be more readily achievable in humans than in rodents or many other species, as human capacity for de novo lipogenesis is relatively low – hence, we truly "wear the fat we eat".[31]

In an intriguing series of investigations, Chan and colleagues have shown that exposure of astrocytes to palmitate or stearate, but not unsaturated fatty acids, induces astrocytes to secrete soluble mediators that can act on neurons to promote tau phosphorylation (via activation of the kinases GSK-3 and cdk5) and stimulate the synthesis of amyloid beta by boosting expression of BACE1.[32-34] The soluble mediators responsible for his phenomenon include tumor necrosis factor-alpha and interleukin-1. Various agents which block ceramide synthesis completely abrogate the impact of palmitate and stearate on astrocyte function. Curiously, palmitate exposure also decreases the capacity of astrocytes to assimilate and metabolize glucose; decreased glucose utilization by astrocytes is now suspected to be at least partially responsible for the decline in brain glucose uptake that characterizes AD. Comparable concentrations of palmitate or stearate failed to modulate neuronal function in the absence of astrocytes, indicating that intraneuronal *de novo* synthesis of ceramide may have little pathogenic potential.[35]

Other investigators, focusing on microglial cells, have likewise demonstrated that exposure of microglia-like cells (THP-1 macrophages) to palmitate or stearate promotes a pro-inflammatory phenotype associated with increased production of cytokines (IL-6, IL-8).[36] Moreover, such exposure markedly potentiates the activating response to lipopolysaccharide exposure, the traditional means of promoting microglial activation. These effects were shown to be mediated by ceramide synthesis and consequent activation of PKC-zeta, leading to downstream activation of the MAP kinases JNK, p38 and Erk; unsaturated fats could not replicate these effects. A subsequent study by other investigators confirmed many of these observations, and further observed that palmitate-treated THP-1 cells were toxic to the SH-SY5Y neuroblastoma cell line.[37] In other recent research , both palmitate and stearate exposure were shown to induce the full range of pro-inflammatory microglial activation in the BV-2 microglial cell line – activation of NF-kappaB, induction of iNOS and Cox-2, increased cytokine production, increased oxidative stress, and increased expression of CD11b. Curiously, an antibody to the TLR4 receptor prevented these activating effects.[38] This study did not examine the role of ceramide production in these effects. The authors conclude that their findings suggest that "nutrition rich in saturated fatty acids may be linked to some inflammatory diseases of the CNS."

In support of the possibility that dietary saturated fat may influence neuroinflammation, a long-term feeding of a diet high in such fats induces NADPH oxidase-associated oxidative stress and markers of

inflammation (increased expression of cox-2 and nuclear NF-kappaB) in the cerebral cortex of rats. Since microglia are the richest source of NADPH oxidase in the brain, these effects are likely to reflect microglial activation. [39]

Speaking in favor of a role of *de novo* ceramide synthesis in neurodegenerative illness, there is recent evidence that protein expression of serine palmitoyltransferase, the rate-limiting enzyme for ceramide synthesis, is elevated in the cortices of AD patients.[40] These findings complement earlier studies demonstrating higher ceramide levels in the brain or CSF of AD patients, and concluding that elevated serum levels of certain ceramides predict increased risk for AD and cognitive impairment.[41-47]

In light of accumulating evidence that long-chain saturated fats are capable of promoting neuroinflammation, it is logical to suspect that this phenomenon may rationalize the protective impact of Mediterranean-type diets on risk for neurodegenerative disorders. And, since persistent neuroinflammation is likely to be a driving force in the neurodegeneration linked to traumatic brain injury, it is reasonable to postulate that diets low in saturated fat could down-regulate such neuroinflammation and hence lessen risk for subsequent neuronal pathology.

It should be noted that a number of other dietary measures appear to have potential for controlling neuroinflammation. A wide range of natural dietary flavonoids – such as those found in green tea, berries, and other fruits – have been shown to antagonize LPS-mediated microglial activation in vitro, and to have an ameliorative impact on various rodent models of neurodegeneration in vivo.[48-57] Recent prospective and cross-sectional epidemiology from Japan suggests that heavy habitual consumption of green tea may have a markedly protective impact on risk for cognitive impairment and dementia in the aged.[58, 59] And limited Western epidemiology suggests that frequent consumption of berries might also slow onset of cognitive impairment.[60, 61] In addition, regular consumption of caffeinated beverages, good vitamin D status, long-chain omega-3 fats, and spirulina appear to have potential for dampening neuroinflammation and staving off neurodegeneration.[62-79] It should be noted that a whole-food plant-based diet is likely to be richer in brain-protective polyphenols than are more typically Western diets high in animal products, refined grains, and added sugars and oils. Arian Foster's adoption of such a diet may be wiser than is generally perceived.

A Postscript

These considerations may help to rationalize the claims of neurologist Roy Swank that a diet exceptionally low in saturated fat has a markedly favorable impact on the clinical course of multiple sclerosis (MS).[80-82] During several decades of clinical work, Swank employed such a diet – sometimes supplemented with unsaturated fats – in numerous MS patients. He reported that, in patients who adopted such a diet within several years of diagnosis, and remained persistently faithful to it, little further clinical deterioration was observed over decades of follow-up. In patients who adopted such a diet at a later stage of their illness, he felt that the rate of their clinical deterioration was slowed. There is now growing evidence that pro-inflammatory activated microglia, macrophages, and reactive astrocytes are largely responsible for the death of oligodendrocytes that underlies this syndrome.[83-91] *De novo* synthesis of ceramide (particularly C16:0-Cer) appears to be a key mediator of macrophage and astrocyte activation in the mouse model of MS, experimental autoimmune encephalomyelitis, and this syndrome is ameliorated by administration of L-cycloserine, an inhibitor of serine palmitoyltransferase.[92, 93] Activation of macrophages by interferon-g, thought to play a key role in the genesis of MS, has been found to be

contingent on induced expression of ceramide synthase 6 (which synthesizes C16:0-Cer); knockdown of this enzyme, or exposure to L-cycloserine, prevents this activation.[92] Moreover, ceramide levels are notably elevated in reactive astrocytes in the active lesions of clinical MS, and CSF levels or C16:0-Cer in MS patients are approximately double those in controls.[92, 93] Hence, the putative success of the Swank diet in MS may reflect a down-regulation of ceramide-driven neuroinflammation in the CNS.

In light of this recent evidence that de novo ceramide synthesis may play a key role in macrophage activation, it would be of interest to know whether this phenomenon is pertinent to the ameliorative impact of low-fat vegan diets on clinical rheumatoid arthritis.[94, 95]

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