Medical Hypotheses 118 (2018) 114–120

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Ferulic acid may target MyD88-mediated pro-inflammatory signaling – Implications for the health protection afforded by whole grains, anthocyanins, and coffee

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ARTICLE INFO

Keywords:
Ferulic acid
MyD88
Toll-like receptors
Interleukin-1 receptor
Whole grains
Anthocyanins
Coffee

ABSTRACT

Higher dietary intakes of anthocyanins have been linked epidemiologically to decreased risk for metabolic syndrome, type 2 diabetes and cardiovascular events; clinical trials and rodent studies evaluating ingestion of anthocyanin-rich extracts confirm favorable effects of these agents on endothelial function and metabolic syndrome. However, these benefits of anthocyanins are lost in rats whose gut microbiome has been eliminated with antibiotic treatment – pointing to bacterial metabolites of anthocyanins as the likely protective agents. A human pharmacokinetic assessment of orally administered cyanidin-3-O-glucoside, a prominent anthocyanin, has revealed that, whereas this compound is minimally absorbed, ferulic acid (FA) is one of its primary metabolites that appears in plasma. FA is a strong antioxidant and phase 2 inducer that has exerted marked anti-inflammatory effects in a number of rodent and cell culture studies; in particular, FA is highly protective in rodent models of diet-induced weight gain and metabolic syndrome. FA, a precursor for lignan synthesis, is widely distributed in plant-based whole foods, mostly in conjugated form; whole grains are a notable source. Coffee ingestion boosts plasma FA owing to gastrointestinal metabolism of chlorogenic acid. Hence, it is reasonable to suspect that FA mediates some of the broad health benefits that have been associated epidemiologically with frequent consumption of whole grains, anthocyanins, coffee, and unrefined plant-based foods. The molecular basis of the anti-inflammatory effects of FA may have been clarified by a recent study demonstrating that FA can target the adaptor protein MyD88; this plays an essential role in pro-inflammatory signaling by most toll-like receptors and interleukin-1β. If feasible oral intakes of FA can indeed down-regulate MyD88-dependent signaling, favorable effects of FA on neurodegeneration, hypothalamic inflammation, weight gain, adipocyte and beta cell function, adiponectin secretion, vascular health, and cartilage and bone integrity can be predicted. Since FA is well tolerated, safe, and natural, it may have great potential as a protective nutraceutical, and clinical trials evaluating its effects are needed.

Ferulic acid may mediate the health benefits of anthocyanins

Nutritional epidemiology has linked relatively high dietary intakes of anthocyanins to decreased risk for metabolic syndrome, type 2 diabetes, and cardiovascular events [1–5]. Clinical trials in which concentrated anthocyanins have been administered have likewise found positive effects on serum lipids, glycemic control, and endothelial and platelet function [6–12]. In rodents, dietary anthocyanins suppress the increase in body fat associated with diets high in fat and/or fructose [13–17]. Moreover, *in vitro* studies have demonstrated anti-inflammatory and insulin-sensitizing properties for cyanidin-3-O-glucoside (C3G), a prominent anthocyanin [18–22]. However, the favorable impact of orally-administered black currant anthocyanins on weight gain in mice fed a high-fat diet is largely lost when the animals are currently administered an antibiotic cocktail that eliminates the gut microbiome [17]. This finding suggests that bacterial metabolites of anthocyanins, as opposed to anthocyanins directly, may mediate many of their protective effects. In a pharmacokinetic study examining the fate of 500 mg of isotopically labeled C3G administered orally to human volunteers, the three most prominent C3G-derived compounds observed in serum were hippuric acid (a conjugate of glycine and benzoic acid), vanillic acid, and ferulic acid; the observed level of intact C3G was far lower, and its half-life in serum was very short compared to that of the three mentioned metabolites (t_{max} = 1.8 h, $t_{1/2}$ = 0.4 h) [23].

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https://doi.org/10.1016/j.mehy.2018.06.032
Received 17 April 2018; Accepted 27 June 2018

Ferulic acid (FA) is of particular interest, inasmuch as this agent has been shown to have anti-inflammatory and antioxidant effects in many rodent studies; in particular, at least 5 rodents studies have reported that weight gain or metabolic syndrome in rodents fed diets rich in fat and/or fructose is markedly ameliorated when FA is concurrently administered [24–29]. In the C3G pharmacokinetic study, the t_{max} for FA was 8.2 h, and its serum half life was 21.4 h; hence, it is reasonable to expect that, if FA is a primary mediator of the benefits of dietary anthocyanins, episodic ingestions of anthocyanins might be expected to have persistent metabolic effects.

Whole plant-based foods are rich in ferulic acid

Ferulic acid, synthesized from tyrosine in plants, is widely distributed in plant-based foods – including whole grains, fruits, vegetables, and legumes – presumably reflecting the fact that it serves as a precursor for lignans, prominent structural components of plants [30,31]. Most of this FA is present as conjugates, linked to saccharides, polysaccharides, or oligosaccharides; in rich bran oil, the gamma-oryzanol present is a conjugate of FA with various phytosterols. The bioavailability of this FA is variable, depending on the susceptibility of FA conjugates to cleavage by digestive esterases or gut microflora; FA conjugated to mono- or oligosaccharides is typically more available than that linked to complex polysaccharides. A diet containing the recommended servings of fruits, vegetables, legumes, and whole grains is estimated to provide 150–250 mg FA per day [30]. The FA content of wheat bran has reasonably good bioavailability, and is concentrated in the aleurone, thought to be the most protective component of wheat bran [32,33]. (Aleurone is also a good source of magnesium and zinc.) Epidemiologically, consumption of whole grains is associated with good vascular and metabolic outcomes, and lower risk for weight gain, as confirmed in numerous *meta*-analyses – whereas refined grain consumption often is associated with poor outcomes in these respects [34–44]. Differences in glycemic index seem unlikely to be primarily responsible for this discrepancy, since, unless whole grains are consumed in a structurally intact form – as in sprouted grain breads – their glycemic index is not markedly lower than that of refined grains (an exception being grains high in soluble fiber, such as oats) [45]. However, whole grains can favorably modulate the production of gastrointestinal hormones (e.g. glucagon-like peptide-1) owing to bacterial fermentation of fiber and resistant starch [46,47].

Gut bacteria synthesize ferulic acid from various phenolic phytochemicals

As we have seen, anthocyanins can be metabolized by gut bacteria to yield absorbable FA. Furthermore, coffee, whether or not it has been decaffeinated, is a rich source of chlorogenic acid, a conjugate of caffeic acid and a saccharide, quinic acid. About a third of this conjugate is degraded in the upper intestinal tract, and the evolved caffeic acid is largely methylated to form FA, before or after absorption, such that serum FA is higher than serum caffeic acid in the hours following coffee ingestion [48]. (Chlorogenic acid is also degraded by bacterial action in the lower gut, but the derived FA tends to reach the serum as dihydro-FA, which is a poorer antioxidant than FA and may not have the same metabolic effects.) Epidemiology has linked heavy coffee consumption to lower risk for diabetes, metabolic syndrome, heart failure, and Parkinson's disease [49–58]. FA analogously is protective in rodent models of induction of metabolic syndrome and Parkinson's disease [24-29,59,60]. (However, caffeine appears to mediate the protection from Parkinson's mediated by coffee, possibly owing to inhibition of adenosine receptors in microglia [61,62].)

Hence, FA, whether directly present in the diet, or produced by bacterial metabolism of chlorogenic acid, anthocyanins, and likely other types of flavonoids and dietary phenols, might be responsible for a significant proportion of the health benefits afforded by plant-based diets rich in phytochemicals. In that regard, the dietary phytochemical index – defined as the percentage of dietary calories provided by plant foods rich in phytochemicals – has been found to correlate inversely with risk for obesity, weight gain, and hypertension in epidemiological studies [63–68].

Could MyD88 be the target of ferulic acids' anti-inflammatory activity?

There is a substantial literature evaluating the antioxidant and anti-inflammatory effects of FA both in cell culture studies and in rodents. One key effect of FA is that of phase 2 induction via activation of nrf2 transcription factors; phase 2 induction increases the expression of a range of antioxidant enzymes, while also boosting glutathione synthesis (via induction of gamma-glutamylcysteine synthase) [69–72]. Owing to its highly conjugated structure, FA can also act as a potent scavenging antioxidant; for this reason, it is employed in Japan as an approved food preservative [31,73]. While these effects may be largely responsible for the antioxidant impact of FA, the range of anti-inflammatory effects documented suggest that FA may have at least one more key target in nutritionally feasible concentrations.

A recent study by Ren and colleagues has yielded a most intriguing insight in this regard [74]. These investigators confirmed that FA administration provides important protection from ischemia-reperfusion-induced brain injury in rats. They followed this up with *in vitro* studies employing PC-12 cells (derived from a pheochromocytoma) in which ischemia was simulated by exposure to sodium dithionite. FA dose-dependently protected PC-12 cells from dithionite-induced apoptosis, and also reversed the impact of simulated ischemia on expression of a number of pro-inflammatory or pro-apoptotic genes. Curiously, if the PC-12 cells were pre-treated with overexpression plasmids coding for MyD88 – a protein which plays a key mediating role in many pro-inflammatory signaling pathways that activate NF-kappaB – the protection afforded from simulated ischemia by FA was nearly abolished. This finding strongly suggests that FA somehow interferes with MyD88 function, in a manner that can be offset by a marked increase in MyD88 expression.

A mediating role for MyD88 in many inflammation-linked pathologies

Myeloid differentiation factor 88 (MyD88) is an adaptor protein for pro-inflammatory signaling triggered by most toll-like receptors (including notably TLR2 and TLR4), as well as for receptors of the interleukin-1 family [75,76]. Alternatively, TLR3 and TLR4 can employ the adaptor protein TRIF to promote synthesis of type 1 interferon and to activate NF-kappaB [77]. MyD88-dependent signaling activates the stress-associated MAP kinases c-Jun N-terminal kinase (JNK) and p38, as well as NF-kappaB; this induces transcription of many pro-inflammatory cytokines through joint activation of AP-1 and NF-kappaB transcription factors [78].

If MyD88 is the key target for FA's anti-inflammatory activity, one would expect it to have limited impact on signaling pathways not dependent on MyD88. TNFα triggers one of those pathways, and we can locate only two studies indicating that FA interferes with TNFα signaling (whereas there are many studies demonstrating that it can suppress TNFα synthesis) [79,80]. However, in these two studies, FA blunted the impact of TNFα on endothelial cells; it is known that, in endothelial cells, TNFα triggers activation of TLR4 by promoting release of HMGB1, and this activation of TLR4 is a key mediator of TNFα's effects [81].

In light of the utility of FA for blunting weight gain induced by high-fat-sugar diets in rodents, it is notable that TLR4 signaling triggered by saturated fatty acids (likely in conjunction with the liver-derived adaptor protein fetuin A [82,83]) plays a key role in the induction of leptin resistance and weight gain in rodents fed such diets; microglial