Spirulina for Prevention and Control of Preeclampsia

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Abstract

The increased oxidative stress that characterizes preeclampsia (PE) may reflect the hormone-like activity of circulating agonists – likely including AT1 receptor autoantibodies and marinobufagenin – which can activate NADPH oxidase in maternal and placental tissues. The consequent oxidant stress may be a primary mediator of the hypertension, endothelial activation, and proteinuria associated with PE, and may also adversely influence placentation by decreasing the invasive capacity of cytotrophoblasts, thereby promoting intrauterine growth retardation. Thus, regardless of the origin or nature of the agonists which drive the syndrome, systemic down-regulation of NAPDH oxidase activity could be expected to ameliorate the clinical course of PE, and possibly aid its prevention by promoting proper placentation. It may be feasible to achieve such down-regulation through ingestion of spirulina; this organism is the richest known natural source of phycocyanobilin, a chromophore that is now known to act as a potent inhibitor of NADPH oxidase, mimicking the physiological activity of free bilirubin in this regard. Because spirulina has long been used safely as a food, and in high doses fails to exert teratogenic or other adverse effects in pregnant rodents, a controlled trial of spirulina ingestion in pregnant women known to be at high risk for preeclampsia may be warranted. An adjunctive possibility is that high-dose folate supplementation might help to mitigate the pathogenic role of peroxynitrite in PE by acting as a scavenger of peroxynitrite-derived radicals.

A Key Role for NADPH Oxidase in the Pathogenesis of Preeclampsia

Numerous studies show that preeclampsia (PE) is associated with increased oxidative stress in the placenta and maternal vasculature.[1-13] This seems likely to reflect, at least in part, increased production and levels of certain humoral factors – including but possibly not limited to AT1 receptor autoantibodies[14-22] and marinobufagenin (MBG)[23-25] – that stimulate NADPH oxidase activity in placental and maternal vascular tissues via membrane receptors. Within the underperfused placenta, ischemia-reperfusion damage may also trigger superoxide production.[26, 27] There is good reason to suspect that the resultant oxidant stress is a key mediator of the characteristic features of PE – maternal hypertension, endothelial activation, proteinuria, and also possibly the shallow trophoblast invasion that results in fetal growth retardation. With respect to cytotrophoblast function, AT1 agonists as well as MBG have been shown to prevent their differentiation to an invasive phenotype,[28, 29] in part by boosting their production of plasminogen activator inhibitor-1 (PAI-1). Although the role of induced oxidative stress in PAI-1 induction via these agonists has not yet been studied in trophoblasts, it is known to be an obligate mediator of PAI-1 induction in other tissues.[30-36] A portion of the adverse impact of oxidative stress on placentation may reflect quenching of nitric oxide, inasmuch as moderate physiological concentrations of nitric oxide have been reported to

suppress apoptosis in syncytiotrophoblast subjected to ischemia-reperfusion injury.[37] Increased apoptosis and necrosis in syncytiotrophoblast is a characteristic of preeclamptic placentas, and results in the release of microparticles into the maternal circulation that are believed to promote systemic inflammation.[38, 39]

NADPH oxidase is likely to be the chief source of the excess oxidant stress associated with PE. Activation of this complex is a key mediator of signaling via AT1,[40-51] and may also be a mediator of the hormone-like signaling induced by interaction of MBG with the sodium pump.[52, 53] In regard to the latter point, it is of interest that resibufogenin, an analog of MBG that appears to block MBG's hormone-like activity (although mimicking its effect on sodium pump activity), has a profound antioxidant effect in MBG-driven hypertension in rats, and markedly alleviates a PE-like syndrome in pregnant rats treated with dexoycorticosterone acetate and a high-salt diet.[54, 55] NADPH oxidase also appears likely to be the primary source of oxidant stress in placenta subjected to ischemia-reperfusion injury, as it mediates oxidant stress in other tissues subjected to ischemia-reperfusion. Moreover, this enzyme complex is expressed in human placenta and in choriocarcinoma cells (derived from trophoblast); in particular, NOX1 has been identified in these tissues.[56-61] NADPH oxidase activation in vascular endothelial, smooth muscle, and glomerular cells could clearly play a mediating role in the hypertension, endothelial activation, and proteinuria that characterize PE.[62-70] The proteinuria observed in PE likely reflects podocyte dysfunction, and it may be relevant that these cells express AT1 receptors as well as NADPH oxidase activity.[68, 71-73]

The circulating agonists which stimulate NADPH oxidase activity in PE presumably either derive from the distressed fetoplacental unit, or are dependent on it, as the maternal symptoms of hypertension and proteinuria remit as soon as delivery occurs. Conceivably, improper placentation evokes the production of these agonists – which in turn might further impair the process of placentation.

Spirulina Consumption for Inhibition of NAPDH Oxidase

Previous efforts to treat or prevent PE with nutritional antioxidants (primarily vitamins C and E) have borne little fruit,[74-77] likely because most such compounds do not influence peroxyitrite production, prevent the quenching of nitric oxide, or modulate the impact of hydrogen peroxide on cell signaling mechanisms. The failure of vitamin E to benefit PE presumably implies that lipid peroxidation is not a major mediator of this syndrome. However, there is now evidence that phycocyanobilin (PCB), which accounts for about 0.6% of the dry weight of spirulina, can act as a potent inhibitor of NADPH oxidase;[78] its activity in this regard appears to mimic the physiological antioxidant role of free bilirubin.[79-82] Moreover, this compound likely has good bioavailability, as feeding of sprirulina (or of phycocyanin, the spirulina protein which includes PCB as a chromophore) has shown profound and versatile anti-inflammatory, cytoprotective, and antiatherogenic activities in rodent studies[78, 83-93] – effects which could be readily explained by partial inhibition of NADPH oxidase.[78, 82] Although little clinical evaluation of spirulina of significance has been accomplished to date, a recent open clinical study reported that feeding 4.5 g spirulina daily to healthy volunteers was

associated with hypolipidemic effects, as well as significant reductions in blood pressure (averaging 11 points systolic, 6 points diastolic).[94] The impact on blood pressure could well reflect inhibition of NADPH oxidase, thus suggesting that PCB may have good bioavailability in humans as it does in rodents. Moreover, this effect is substantial, when one considers that only a minority of the subjects in this study were considered hypertensive.

Spirulina was used as a traditional food by the Aztecs, and is still used for that purpose by Africans living near Lake Chad.[95, 96] Within the last 30 years, spirulina has been popularized as supplemental food among "healthfood" consumers, consumed as a powder or in tablets. Toxicological studies in rodents have failed to note any adverse effects when spirulina is fed in substantial quantities;[97] in particular, no teratogenicity or other adverse effects have been noted when spirulina is fed to pregnant mice or rats.[98-100] In light of the understandable reluctance to prescribe drugs during pregnancy, the possibility of using a healthful whole food in the prevention and management of PE is particularly appealing. If indeed excess activation of NAPDH oxidase plays a key role in the pathogenesis and complications of PE – as seems likely in light of current evidence – a controlled clinical study examining the impact of dietary spirulina in pregnant women known to be at high risk for PE appears to be warranted.

High-Dose Folate vs. Peroxynitrite

An additional possibility for managing PE is suggested by evidence that peroxynitrite production is elevated in this disorder, and may contribute to vascular dysfunction via PARP activation.[2, 12, 101-103] It is now known that the chief physiological metabolite of dietary folic acid, 5-methyltetrahydrofolate, acts as an efficient scavenger for potent oxidants derived from peroxynitrite[104-106] – such as those which induce nitrotyrosine formation and PARP activation. Moreover, the level of 5-methyltetrahydrofolate can be increased quite markedly in most tissues (though probably not the brain) by high-dose folate supplementation.[105, 106] This effect presumably explains the ability of high-dose folate to prevent oxidation of tetrahydrobiopterin and restore normal coupling of eNOS in inflamed vascular endothelium.[105, 107-110] Thus, it is reasonable to predict that high-dose folate could favorably influence that portion of PE pathogenesis that is mediated by peroxynitrite production.

Previous clinical research has established that supplemental calcium can reduce risk for preeclampsia[111, 112], and there is more recent evidence that good vitamin D status is also associated with lessened risk.[111, 113] Moreover, poor selenium status may increase PE risk[114-116] – a finding that is consistent with the role of selenium-dependent peroxidases in blunting modulation of signal transduction by peroxides, and concordant with a role for oxidant stress in mediation of this disorder. There thus may be considerable scope for reducing risk for PE, and decreasing the severity of this disorder when it does occur, by employing appropriate nutritional measures throughout pregnancy.

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