β-Boswellic Acid, A Safe and Clinically Effective Inhibitor of Prostaglandin E Synthase-1, Has Potential for Prevention of Cancer, Alzheimer's Disease, and Vascular Disorders, and for Control of Inflammatory Pain

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Abstract

Boswellia serrata gum resin –a.k.a. frankincense – has traditionally been used as an anti-inflammatory agent in Ayurvedic medicine. More recently, extracts of this resin enriched in boswellic acids have demonstrated anti-inflammatory properties in rodents and beneficial clinical effects in arthritis, colitis, and brain edema, without notable side effects. Although initial reports suggested that the clinical utilty of boswellic acids might reflect inhibition of 5-lipoxygenase, more recent studies pinpoint microsomal prostaglandin E synthase-1 (mPGES-1) as their likely target. This raises the intriguing prospect that boswellic acids, by inhibiting PGE2 production at a distal level – so that production of protective prostacyclin is not blocked - might provide many of the therapeutic and preventive benefits associated with cyclooxygenase inhibitors, without the toxic risks entailed by these drugs. Regular use of NSAIDs or aspirin has been associated with a modest reduction in risk for many cancers, and markedly lower risk for Alzheimers disease (albeit these agents are not therapeutically useful in the latter); there is reason to suspect that a suppression of mPGES-1-mediated PGE2 production may be largely responsible for these protective effects. mPGES-1 knockout mice appear to be less prone to atherosclerosis, experience less brain trauma following stroke, and do not develop the gastrointestinal or renal lesions associated with use of non-specific cyclooxygenase inhibitors; they are also protected in models of inflammatory hyperalgesia. If further studies confirm that boswellic acids can function clinically as mPGES-1 inhibitors, there will be reason to suspect that these safe natural agents will have utility in the prevention of Alzheimer's disease and many cancers, without adverse consequences for the GI tract, kidneys, or vascular system, and will also be useful in the management of cancer and inflammatory hyperalgesia.

Microsomal Prostaglandin E Synthase-1 May be the Key Target of Boswellic Acids

The gum resin of Boswellia serrata – more popularly known as frankincense – have been used traditionally in Ayurvedic medicine for treatment of inflammatory disorders. More recently, extracts of this resin enriched in pentacyclic triterpenoids known as boswellic acids have been employed as anti-inflammatory nutraceuticals.[1, 2] Pilot clinical studies do indeed suggest that such extracts can promote pain control and dampen inflammation in osteoarthritis and colitis, and help to control the brain edema associated with radiotherapy of cerebral tumors; anti-inflammatory effects in rodent models have also been demonstrated.[3-12] The most prominent of the boswellic acids in frankincense is beta-boswellic acid; the other boswellic acids are derived by addition of a ketone group and/or an acetyl group to beta-boswellic acid.

Initial attempts to clarify the molecular target of boswellic acids in inflammatory disorders determined that keto-boswellic acids can inhibit 5-lipoxygenase in low micromolar concentrations.[13-16] This suggested that boswellic acid preparations might dampen inflammation by blocking leukotriene synthesis,

and led to the development of nutraceutical preparations selectively enriched in keto-boswellic acids – most notably 3-acetyl-11-keto-beta-boswellic acid (AKBA). However, subsequent research has cast considerable doubt on the thesis that 5-lipoxygenase inhibition mediates the clinical anti-inflammatory activity of boswellic acids.[17] In particular, the keto-boswellic acids appear to be inefficiently absorbed, such that the plasma concentrations measured after oral administration of standard clinical doses of boswellia extracts are in the sub-micromolar range – too low to achieve effective inhibition of 5-lipoxygenase in vitro; in contrast, steady state levels of beta-boswellic acid of around 10 μM have been measured in these studies.[18, 19] Moreover, AKBA fails to inhibit 5-lipoxygenase activity in whole blood in vitro, apparently owing to a high affinity of AKBA for albumin.[17] No reduction in plasma levels of leukotriene B4 was noted in humans after an 800 mg oral dose of a boswellic acid-rich extract of boswellia, and there do not appear to be any reports that boswellic acids can modulate leukotriene levels *in vivo*.[17] Also pertinent is the fact that leukotrienes are not thought to play a prominent role in the pathogenesis of the disorders – colitis and osteoarthritis – reported to respond to boswellic acids clinically.[17] These perplexing observations motivated the search for alternative molecular targets which might account for the clinical utility of boswellic acids.

Recently, Werz and colleagues have published a most fascinating discovery – in low micromolar concentrations, AKBA, beta-boswellic acid, and 11-keto-beta-boswellic acid are capable of inhibiting microsomal prostaglandin E synthase-1 (mPGES-1), with IC_{50} values of 3, 5 and 10 μM, respectively.[20] In whole blood, beta-boswellic acid achieved this inhibition with an IC50 of about 10 μM – comparable to steady-state plasma levels measured during oral clinical administration of boswellic acids – whereas the keto derivatives were ineffective, likely owing to the albumin binding previously mentioned. In rodent models of inflammation, oral or intraperitoneal administration of beta-boswellic acid (1 mg/kg) both dampened the inflammation and suppressed the level of PGE2 in inflamed tissue; the keto derivatives showed minimal activity in this regard. There is therefore good reason to suspect that inhibition of mPGES-1-mediated synthesis of PGE2 is largely responsible for the useful clinical effects of boswellic acids. Notably, PGE2 is suspected to play a pathogenic role in each of the clinical syndromes reported to respond to these agents.[21-26]

mPGES-1 is one of three known enzymes capable of converting PGH2 – the product of cyclooxygenase activity – to PGE2.[27] The other two – microsomal PGE synthase-2 and cytoplasmic PGE synthase – tend to be constitutively expressed at low levels in cells, whereas mPGES-1 is markedly inducible by pro-inflammatory cytokines in concert with cyclooxygenase-2 (cox-2). Moreover, cox-2 and mPGES-1 are usually functionally coupled, such that mPGES-1 acts preferentially on the PGH2 produced by cox-2.[28] For this reason, most of the PGE2 generated in inflamed tissues is produced via mPGES-1. The implication is that beta-boswellic acid may be especially effective for suppressing PGE2 production in the context of inflammation.

Cox-2 and mPGES-1 Collaborate in Cancer Induction and Spread

Owing to the facts that NSAIDS and aspirin have been in widespread use for many decades as analgesic and anti-inflammatory agents, and that low-dose aspirin has been studied in many huge randomized clinical trials to assess its impact on vascular events, epidemiologists are now able to assess the impact of prolonged NSAID/aspirin use on risk for a wide range of disorders. Two findings that have emerged from such studies are particularly striking. NSAID use and daily low-dose aspirin have been linked to a

modest but significant reduction in risk for many types of cancer, particular adenocarcinomas, in a number of meta-analyses.[29-47] The findings with low-dose aspirin, derived from meta-analyses of randomized trials, are particularly compelling;[44-47] inhibition of cox-2 appears likely to mediate this effect, as low-dose aspirin was found not to impact risk for colorectal cancers that fail to express this enzyme.[44] In subjects who did develop cancers during administration of low-dose aspirin, risk for distant metastases was significantly lower than in subjects who developed cancer in the placebo groups.[48] Habitual NSAID use has also been associated with a marked reduction in risk for Alzheimer's disease (AD) – in those who have used NSAIDS for a number of years, this reduction in risk may be 50% or greater.[49-51] There is reason to suspect that a reduction of PGE2 production may be largely responsible for these protective effects.

There is a considerable research literature addressing the role of increased cox-2 expression in the induction and progression of many types of cancer; PGE2, acting via its characteristic receptors EP1-4, is strongly suspected to mediate much of the pathogenic impact of cox-2 in this regard.[52, 53] Cox-2-derived PGE2 is reported in various studies to boost cancer cell proliferation, suppress cancer cell apoptosis, promote metastasis, angiogenesis and lymphagiogenesis, and impede immunological rejection of cancer.[54-65] Cox-2 activity both in cancer cells and in the surrounding stroma participates in these effects. Moreover, several studies have demonstrated a role for mPGES-1 in these phenomena.[66, 67] Knockdown of this enzyme in lung, prostate, hepatic, and glioma cancer cell lines notably quells their aggressiveness in vitro and in vivo, and, in mice homozygous for mPEGS-1 knock-out, intestinal tumorigenesis is suppressed;[68-71] (One study however reported an opposite result in this regard[72]). In esophageal and prostate adenocarcinoma cell lines, inhibiting mPGES-1 by a variety of techniques suppresses proliferation and boosts apoptosis.[73, 74] Moreover, transplanted Lewis lung carcinomas and colorectal adenocarcinomas grow less aggressively in mPGES-1 knock-out mice, indicative of a role for stromal expression of this enzyme in cancer progression.[75, 76] When mice are irradiated and transplanted with bone marrow derived from either wild-type or mPGES-1 knockout mice, the growth of implanted Lewis lung carcinoma is impeded in mice receiving the mPGES-1 knockout marrow.[77]

These findings accord nicely with reports indicating that administration of boswellic acids to nude mice can suppress the growth and spread of implanted human pancreatic, prostatic, and colorectal cancers.[78-81] Clinically, oral administration of boswellic acid preparations has been shown to lessen cerebral edema following irradiation of brain tumors;[12, 82] indeed, several reports suggest that cox-2 and PGE2 can mediate brain edema associated with gliomas, radiotherapy, or hemorrhage.[83-86] Hence, boswellic acids may have potential both for cancer prevention, and as adjuvants for cancer therapy.

mPGES-1 May Play a "Kindling" Role in the Onset of Alzheimer's Disease

The findings in regard to AD are slightly perplexing, inasmuch as NSAID therapy has failed to slow the progression of this disorder in patients who are already experiencing memory loss[87] – despite trenchant evidence that NSAIDs can prevent or postpone onset of this disorder in people who are not yet symptomatic. Perhaps we should view cyclooxygenase activity as "kindling" that helps initiate an inflammatory process that then takes on a life of its own, capable of persisting in the absence of cyclooxygenase products. (By analogy, blowing out the match will do little good once the forest is ablaze!)

Athough it is not yet clear which cyclooxygenase products help to trigger AD, strong suspicion has been cast on PGE2. This is elevated in the cerebrospinal fluid of patients with early AD, and increased expression of mPGES-1 has been observed in middle frontal gyrus tissue of AD patients.[88, 89] In two rodent models of AD, amyloid beta expression was notably lower in 8-month-old mice homozygous for knockout of the EP3 receptor, associated with a reduction in beta-secretase activity.[90] Markers of inflammation and oxidative stress were also lower in these knockout mice. The neurotoxicity of microglia exposed to amyloid beta is mitigated if these microglia are derived from EP2 knockout mice.[91] Moreover, EP2 signaling impairs the capacity of microglia to phagocytize amyloid beta; irradiation of transgenic AD model mice and engraftment with marrow cells derived from EP2 knockout donors inhibits brain accumulation of amyloid beta.[92, 93] And primary cerebral neuronal cells derived from mice homozygous for mPGES-1 knockout are protected from the cytotoxicity of an amyloid beta protein fragment (31-35) that induces apoptosis in wild-type neuronal cells.[94] These findings are consistent with a role for mPGES-1-derived PGE2 in the pathgenesis of AD.

It would be of particular interest to breed AD model mice that were also homozygous for mPGES-1 knockout; this might provide further insight into the role of this enzyme in AD pathogenesis - and the potential of boswellic acids for influencing AD risk. So far, no studies have examined the impact on boswellic acids on AD model mice. But it is encouraging that beta-boswellic acid has been shown to have good access to the brain after oral administration in rats.[95]

mPGES-1 Inhibition May Protect Vascular Health and Promote Stroke Recovery

Despite compelling evidence that NSAIDS can reduce risk for AD, and help to prevent and control certain cancers, the employment of these agents for primary prevention has been stymied by their toxicities. As is well known, non-selective cox inhibitors tend to provoke dangerous GI bleeding, as well as renal damage, especially if used in high doses for prolonged periods. This reflects the fact that PGE2 and prostacyclin function physiologically to protect the GI mucosa and kidneys. Cox-2-specific inhibitors did indeed largely succeed in avoiding these side effects – owing to the fact that cox-1 is the primary source of prostanoids in healthy GI mucosa and kidney - but recent epidemiology and careful analysis of clinical trials has revealed that these agents notably increase risk for heart attack and stroke.[96, 97] It is now known that cox-2, expressed constitutively in vascular endothelium, provides a large portion of the PGH2 required for endothelial production of prostacyclin; hence, cox-2 inhibitors tend to suppress vascular prostacyclin production, and thereby promote thrombosis, vasoconstriction, and atherosclerosis.[98] Increased arterial production of leukotrienes – reflecting increased availability of arachidonic acid when cox-2 is inhibited - may also play a role in the cardiovascular toxicity of cox-2 inhibitors.[99] (Non-specific cox inhibitors are less dangerous for vascular health because they concurrently inhibit platelet thromboxane production – a countervailing protective effect.)

There is strong reason to suspect that mPGES-1 inhibitors should be substantially safer than cox inhibitors.[27, 100, 101] mPGES-1 inhibition does not suppress prostacyclin synthesis – if anything, it would be expected to up-regulate it a bit by increasing PGH2 levels – nor does it boost leukotriene production. Prostacyclin, as well as PGE2 produced by the constitutive forms of PGE synthase, can provide protection to the GI tract and kidneys; this presumably explains why mPGES-1 inhibition does not provoke GI lesions in mice, and mPGES-1 knockout mice do not appear to be at increased risk for GI or renal damage.[101, 102] Notably, therapeutic use of boswellic acids has not been associated with GI or renal

toxicity; indeed, these agents are reported to be protective in rodent models of gastric ulceration.[103] To evaluate the impact of mPGES-1 on vascular health, mice prone to atherogenesis (LDL receptor knockouts) were crossbred with mPGES-1 knockout mice to generate mice lacking both LDL receptors and mPGES-1.[104] As compared to LDL receptor knockout expressing normal mPGES-1 activity, the double knockouts developed less severe atheroma that was characterized by a lesser number of macrophages and a greater number of smooth muscle cells – presumably indicative of greater plaque stability. Moreover, urinary prostacyclin metabolites – but not those of thromboxane - were increased in the double knockout mice, presumably reflecting selective up-regulation of prostacyclin production. This suggests that, as opposed to cox-2-specific inhibitors, mPGES-1 inhibitors might actually have a *favorable* impact on progression of atherosclerosis and risk for vascular events.

Moreover, there is evidence that mPGES-1 is a mediator of the brain damage induced by stroke. This enzyme is induced in the ischemic region following a stroke, giving rise to increased PGE2 production.[105] After induction of transient focal brain ischemia, mPGES-1 knockout mice experienced less neuronal apoptosis, brain edema, and neurological dysfunction than wild-type mice.[106] The adverse impact of PGE2 in this setting appears to be mediated by the EP3 receptor.[107] mPGES-1 inhibition may hence be prudent in individuals at risk for stroke. However, with respect to myocardial infarction, mPGES-1 knockout mice subjected to temporary cardiac ischemia are more prone to develop eccentric cardiac myocyte hypertrophy and impaired left ventricular contractile function in the subsequent month, apparently owing to a loss of protective PGE2 activity provided by infiltrating leukocytes.[108, 109] This suggests that mPGES-1 inhibition might be contraindicated for at least several weeks following a myocardial infarct.

A Key Role for mPGES-1 in Inflammatory Hyperalgesia

NSAIDs are commonly used for their analgesic effects. This reflects a role for PGE2 in pain transmission and induction of inflammation. However, prostacyclin is also active in these respects, and constitutive PGE synthases can produce PGE2. To assess the role of mPGES-1 in inflammatory pain models, mPGES-1 knockout mice were compared with wild-type mice in these models.[110] The knockout mice were less responsive in the acetic acid-induced writhing test – indicative of a reduction in perceived pain – and were notably protected from the inflammation associated with collagen-induced arthritis (a model for human rheumatoid arthritis). But their perception of acute thermal pain was no different than that of control mice – consistent with the fact that the role of PGE2 in pain induction is specific to inflammatory pain.[111] These findings accord nicely with the symptomatic benefits associated with boswellic acid therapy in arthritis.

Beta-Boswellic Acid May Have Potential for Primary Prevention

In overview, there is good reason to believe that mPGES-1-mediated PGE2 production plays a key pathogenic role in the induction and progression of many cancers, and in the mediation of inflammation and inflammatory pain. There is also suggestive evidence that the protective impact of NSAID treatment on AD risk is mediated, at least in part, by a suppression of mPGES-1-mediated PGE2 synthesis. As compared to non-selective or cox-2-selective NSAIDs, mPGES-1 inhibitors would not be expected to damage the GI mucosa or kidneys, or increase risk for atheroma and vascular events; indeed, such inhibitors might have a favorable impact on vascular health (save in the immediate aftermath of myocardial infarction).

In light of these considerations, the recent evidence that clinical doses of boswellic acids may function as safe and well tolerated inhibitors of mPGES-1 is of great interest. Further studies, both in rodents and in humans, should evaluate the impact of boswellic acids on PGE2 production, to provide further confirmation for the intriguing findings of Werz and colleagues. And boswellic acids should be evaluated in rodent models of AD, cancer induction, and atherogenesis. Development of nutraceutical boswellia extracts specifically enriched in beta-boswellic acid may also be appropriate. The possibility that these safe, natural and affordable agents – used for centuries in traditional medicine - may be useful for the prevention of cancer, vascular disease, and AD, while also aiding control of pain and inflammation, is exciting indeed.

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