

Preliminary Study/Report

Borage oil reduction of rheumatoid arthritis activity may be mediated by increased cAMP that suppresses tumor necrosis factor-alpha

Richard E. Kast *

Department of Psychiatry, College of Medicine, University of Vermont, Burlington, VT 05401, USA

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Abstract

Recent double blind studies have shown some benefit of borage oil in treatment of rheumatoid arthritis. Tumor necrosis factor-alpha has been shown to be a central mediator of inflammatory and joint destructive processes in rheumatoid arthritis. In this paper, evidence from published research is reviewed that indicates gamma linolenic acid component of borage oil increases prostaglandin E levels that increase cAMP levels that in turn suppress tumor necrosis factor-alpha synthesis. If this biochemical path of borage oil is correct then (1) concomitant non-steroidal anti-inflammatory drug use would tend to undermine borage oil effects, and (2) borage oil would be contraindicated in pregnancy given the teratogenic and labor inducing effects of prostaglandin E agonists. © 2001 Published by Elsevier Science B.V.

Keywords: Borage oil; Cyclic adenosine monophosphate; Inflammation; Prostaglandin E; Rheumatoid arthritis; Tumor necrosis-alpha

1. Introduction

In this short note, I outline the physiologic path by which borage oil, B, might lower tumor necrosis factor-alpha, TNF-alpha, levels. Two corollaries to that physiology are explained: (1) Why patients opting for B treatment of disease that is mediated by increased TNF should avoid non-steroidal anti-inflammatory drugs, NSAIDs, and (2) why B use is contraindicated in pregnancy.

2. Borage oil

B is the oil extracted from the seeds of *Borago officinalis*. It contains about 25% gamma linolenic acid (18:3n-6), GLA. Decreased TNF-alpha after B use or tissue exposure to the extracted GLA is suspected [1]. B and GLA have been shown in several animal models to increase prostaglandin E series levels [1–6]. The suspected path by which GLA does this is outlined in Fig. 1.

3. Prostaglandin and TNF

Many studies have documented an inverse relationship between PGE and TNF-alpha levels [7].

* Tel.: +1-802-863-2462; fax: +1-802-775-3307.
E-mail address: rekast@email.com (R.E. Kast).

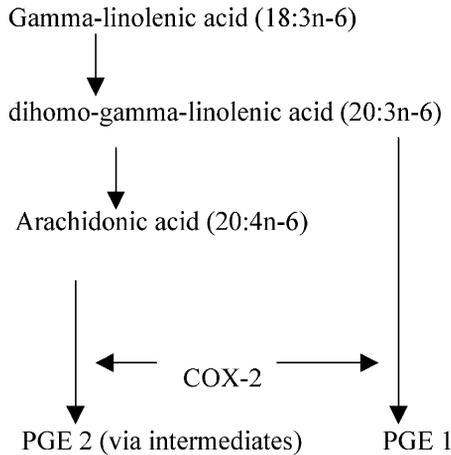


Fig. 1. The path, presented here in simplified form, by which borage oil, 25% of which is gamma-linolenic acid, increases prostaglandin E levels (reviewed in Refs. [10,11]). COX-2 = (inducible) cyclooxygenase-2, catalyses the rate limiting step in prostaglandin synthesis.

Recent work has highlighted the role of intracellular cyclic adenosine monophosphate, cAMP, in control of TNF-alpha synthesis [8,9]. Multiple cAMP elevating maneuvers suppress TNF-alpha synthesis and

cAMP lowering agents reliably raise TNF-alpha levels (reviewed in Ref. [8]). The precise mechanism by which cAMP levels inversely control TNF-alpha is unknown but preliminary evidence points to action at the level of transcriptional control of the TNF-alpha gene. A large body of evidence shows that PGE elevates cAMP, though how it does so is less clear, but probably by allosteric change of adenylate cyclase. PGE-mediated cAMP increase is thought to lower TNF-alpha levels after B or GLA administration. The cAMP/PGE control cycle for TNF-alpha from Ref. [8] is outlined in Fig. 2.

4. TNF and rheumatoid arthritis

TNF-alpha is thought to be a central tissue destructive mediator in rheumatoid arthritis, RA. Although B and GLA are occasionally used to treat RA, such use is currently considered peripheral, their clinical utility unproven, and risks unidentified. There are two double blind, placebo controlled trials of B in RA from 1993 and 1996. A small but clinically meaningful and statistically significant lowering of

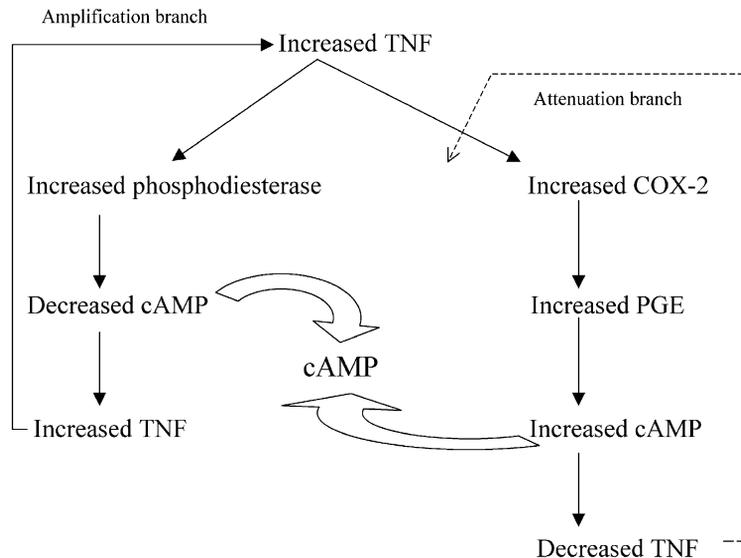


Fig. 2. Amplification and attenuation feedback cycles centered on opposing effects on cAMP that a given increase in TNF could have. Relative weighting of attenuation or amplification branches are determined by other factors intersecting the elements of the two branches (see Ref. [8] for details).

RA disease activity by daily oral administration of 1.4 g of GLA [10] and 2.8-g GLA [11] were documented. Continuing easing of RA signs and symptoms were noted at the end of the study at 12 months [11]. Zurier et al. note [11] B may thus be a disease modifying anti-rheumatic drug, DMARD. Trials in various rheumatologic diseases and GLA's TNF-alpha lowering effects were recently reviewed [1].

5. Warnings

NSAID effects of raising TNF-alpha levels through suppression of PGE by cyclooxygenase inhibition, was recently reviewed [9]. Unless the biochemistry of B's suppression of TNF-alpha presented here is shown to be incorrect, patients choosing B as an alternative treatment of RA should be advised to avoid NSAIDs. By inhibition of cyclooxygenase in the rate-limiting step of prostaglandin synthesis, the PGE raising and hence TNF-alpha lowering effects of B would be diminished by an NSAID.

Prostaglandins have profound effects on parturition. PGE analogues like misoprostol induce abortion early in pregnancy [12], induce labor near term [13], and are probably teratogenic in the first trimester [14]. B use is contraindicated in pregnancy or in women with potential to become pregnant. The effects of prolonged B use or other prostaglandin increasing interventions have not been studied. Indeed, careful short-term toxicity studies with B have not been done, although no toxicity concerns are apparent so far. Both studies would be required before borage oil could be considered a first line immunomodulating pharmaceutical agent for use in RA.

DMARDs are few. None currently available seem to have as benign a side effect profile as B. Given B's good tolerability, widespread accessibility, and low short-term side effect burden, it would seem further studies on B or GLA would be warranted in diseases like RA where TNF-alpha is thought to be a central pathophysiological mediator.

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