Essential Fatty Acid Therapy in Canine Atopic Dermatitis and Cancer: a brief review

Introduction

Essential polyunsaturated fatty acids have a proven therapeutic benefit in the treatment of canine atopic dermatitis and may be useful in the management of canine cancer.

What the correct dose is and what combinations of oils are the best has been the subject of doubt and confusion. In the case of canine atopic dermatitis, there is now a large body of literature on which some recommendations can be based.

In the case of cancer, the role of COX-2 inhibition in cancer treatment is right on the cutting edge. Definitive clinical trials are just beginning in man and animals but there seems little reason to deny our patients the potential benefits.

Essential polyunsaturated acid metabolism

We need to look a little at the biochemistry of essential fatty acids. Omega-6 and omega-3 fatty acids are so called based on the position of the first double bond in the fatty acid chain. Fatty acids are described by a formula. For example, omega-6 arachidonic acid is 20:3:N6 meaning that there are twenty carbons in the chain, four double bonds beginning at position six. It is best to examine omega-6 and omega-3 fatty acid metabolism separately.

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The Omega-6 Story

Linoleic acid 18:2:N6 (**LA**) is an essential polyunsaturated fatty acid found in most dog foods. It is converted by 6-desaturase by the addition of a further double bond to gamma-linolenic acid 18:3:N6 (**GLA**) . Three things are important here:

1) GLA is an omega-6 and must not be confused with alpha-linolenic acid, an omerga-3 that we will meet later.
2) The skin, unlike most other body cells, lacks most of the fatty acid desaturase enzymes, thus desaturating steps in fatty acid metabolism occur largely extra-cutaneously.
3) GLA is found in a number of oils used in Veterinary medicine, particularly evening primrose oil, borage seed oil and black current oil.

GLA is elongated to dihomo-GLA 20:N6 and then can go one of two ways:

1) Further extra-cutaneous desaturation to arachidonic acid 20:4:N6 (**AA**) Acted on by cyclo-oxigenase-1 and 2 (**COX-1** and **COX-2**) and lipoxygenase (**LPO**)

When dihomo-GLA is acted on by COX it competes for this enzyme with AA. AA is stored in cell membranes and released in response to inflammation. The release of AA

from cell membranes is an active process catalyzed by a phospholipase. Inhibition of this phospholipase is one of the many anti-inflammatory actions of corticosteroids.

The products of COX and LPO action , after a series of steps are called **eicosanoids**. Simply, but not completely, the eicosanoids produced when COX-1 acts on AA are protective to the stomach, kidney and other organs and those produced by COX-2 and LPO are inflammatory mediators.

When COX-2 and LPO act on dihomo-GLA a series of anti-inflammatory or less-inflammatory eicosanoids are produced. The anti-inflammatory effect of dihomo-GLA , is it's ability to compete with AA for available COX-2 and LPO.

The Omega-3 Story

The most common source of omega-3 fatty acid is dietary alpha-linolenic acid (**ALA**). Remember this stuff is different to GLA, an omega-6 fatty acid. ALA is present in relatively small amounts in most dog food, including the premium brands. Flax seed oil is a rich source of ALA. ALA is desaturated to eicosapentaenoic acid 20:5:N3 (**EPA**) and this in turn is desaturated and elongated to docosahexaenoic acid 22:6:N3 (**DHA**). Fish oil is a rich source of EPA and DHA. EPA is a strong competitor with AA for COX-2 and LPO, also resulting in a series of anti-inflammatory or less- inflammatory eicosanoids. The quality of a fish oil as an anti-inflammatory product is best expressed in terms of it's EPA content.

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In theory, one would deduce that some form of combination supplement of GLA and ALA/EPA would be the best to get a "double banger" COX-2/LPO competition but the literature in the case of canine atopic dermatitis does not support this.

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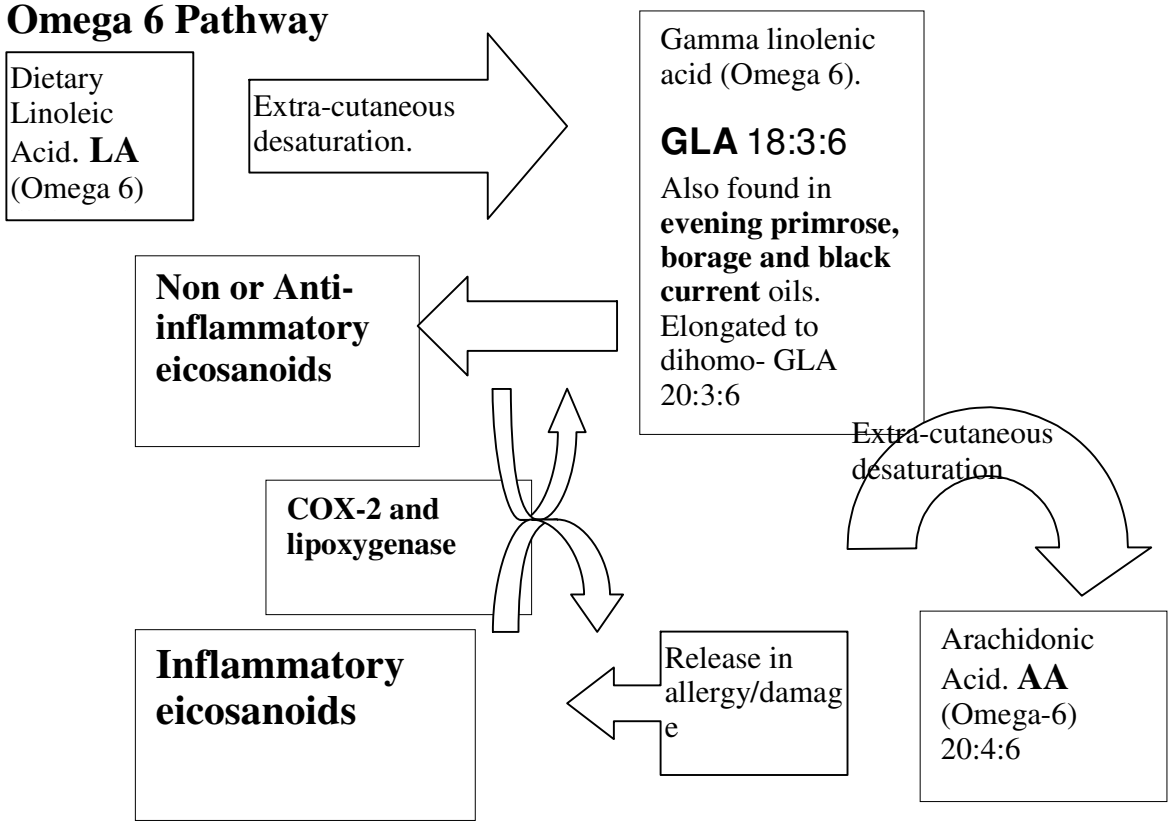
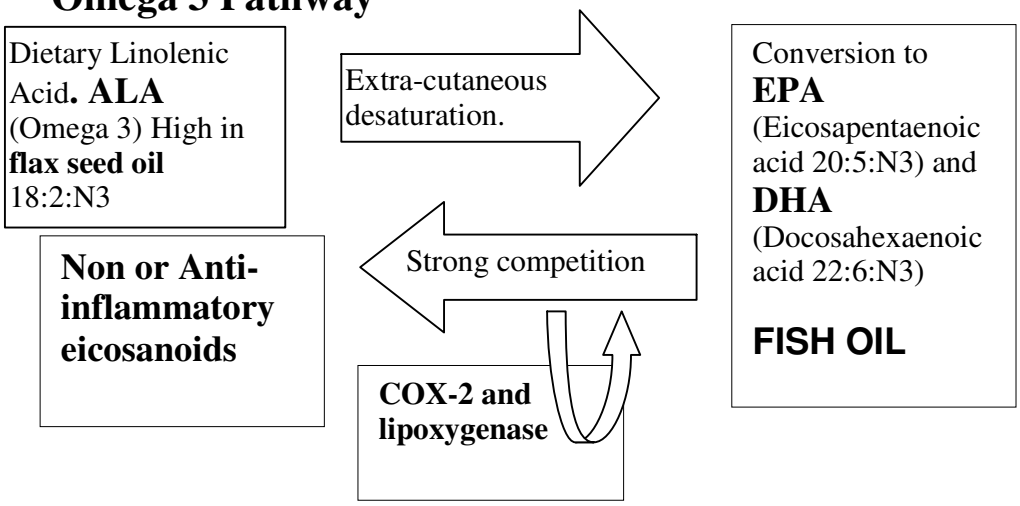
1) Omega 6 Pathway



Omega 3 Pathway



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The current state of evidence in canine atopic dermatitis is that:

The dose of 40-50mg of EPA/kg/day (eqivilent to 1ml of cold water marine fish oil per 4kg of body weight) has been shown in multiple studies to be effective in reducing pruritis in canine atopic dermatitis [3] [4].

About 15-20% of atopic dogs can be controlled with fatty acid therapy alone while a significant proportion of others have a reduction in pruritis that permits reduction of cortisone doses [4] [8] [10]. Even dogs not obviously responding to fatty acid supplement alone can be treated with lower doses of prednisolone [2].

There is a variability in the biochemical response between atopic dogs to fatty acid supplementation [3]. Dogs responding may represent a destinct biological subset [11].

There is no correlation between response and the N6:N3 ratio, response and increased dose and response and type of base diet supplemented. There is no correlation between plasma fatty acid profiles, N3/N6 ratio fed or response [1] [4] [5]. Atopic dogs do not lack LA desaturases, as in atopic people, and serum fatty acid profiles are no different between normal and atopic dogs [7].

There is no correlation between response to therapy and age, breed , sex , duration of disease or number of positive intradermal tests[10].

Withdrawal of poliunsaturated fatty acid therapy and substitution with a control diet in dogs responding to N3-N6 therapy results in deterioration. [1] [11].

Eveing primrose oil , a source of omega-6 GLA, is effective in reducing pruritis when compared to control dogs [9].

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Most dog fooods supplemeted with poliunsaturated fatty acids contain high levels of linoleic acid (LA). High dose supplementation of linoleic acid in the form of corn oil (90% LA and 10%GLA) is markedly inferior to the response to standard doses of cold water marine fish oil. [3]. Supplements rich in LA, such as cooking oils, increase skin luster and reduce scale and may increase the effectiveness of the epidermal barrier. Even very low dose supplementation of a diet high in LA can be effective. When a combination borage seed/ fish oil supplement (aprox N6:N3 ratio 17:1) was given to dogs fed a diet of 3.9% poliunsaturated fat but with 90% of thse being LA there was a response to low doses of the supplement at a low dose (0.6ml/10kg). This was despite the supplement being 61% LA and only 34% GLA and 7% N3 (EPA + DHA) [8].

There is a lag phase for the effect of poliunsaturated fatty acid therapy of between 4-12 weeks until maximal bendefits are reached [8]. Flax seed oil (ALA source) used for one month was no better than the control sunflower seed oil (LA source) [6]. Flax seed oil was as effective as fish oil when used for 10 weeks [4].

The response to fatty acid suppplement must be seperated from the response to infection control in evaluating uncontrolled studies [5].

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Cancer

Essential poliunsaturated fatty acids may be of value in cancer therapy both as inhibitors of COX-2 and also as a non-carbohydrate calorie source.

Cancer cells produce high levels of COX-2. In humans, many NSAIDs have been shown assist treatment in a large number of cancers[2 7]. Much of this work has been done in humans, but it translates to animals. There is now a vast literature on this topic. Tumour cell cyclo-oxigenase-2 (COX-2) is induced in many canine cancers[1 3 6]. Indeed nearly all canine tumours studied to date, just as in man, show high levels of COX-2 expression relative to their parent tissue. Piroxicam has been used to treat canine transitional cell bladder cancer. Prixicam's action is probably as NSAID[3] rather than the any other property of the drug itself and there is no evidence to support the use of this toxic drug over registered COX-2 specific NSAIDs.

COX-2 uses arachidonic acid as a substrate resulting in the production of inflammatory prostaglandins and thromboxanes and these are required for tumour invasion and new blood vessel growth. COX-2 inhibits tumour angiogenesis at multiple points in the angiogenic cascade. COX-2 inhibitor therapy should have at least additive effects when combined with other therapy such as chemotherapy or radiation[2] and the same can be argued for polyunsaturated fatty acid supplementation.

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Tumour cells preferentially use of carbohydrate as an energy source and poor capacity to metabolise lipids. Diets low in carbohydrates and high in fat, especially omerga-3, benefit cancer patients [4 5]. This benefit may be relate to COX-2 inhibition, nutrition or both. The aim of the higher dose of omerga-3 oil is completion for COX-2 and lipoxygenase with arachidonic acid, providing anti-inflammatory and anti-neoplastic (COX-2) effects, and supplying a lipid calorie source. The optimum anti-neoplastic dose and N6/N3 ratio still awaits further controlled clinical trials.

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Summary

1. Dogs with atopic dermatitis respond to EFA (essential fatty acid) supplementation in a spectrum from:
   - Complete control of symptoms
   - Reduction in pruritus
   - Reduction in the amount of steroid required for control (with or without visible response to the EFA's)
   - No response at all.
2. The time lag for benefits to reach maximum may be anywhere up to 12 weeks and no benefits may be seen for 8 weeks.
3. There is no proven optimal N6:N3 ratio or total dose of EFA's. There is a base dose beyond which no benefit occurs but what this base dose for any combination is is unknown. There is no proven superior combination of oils. There is a consistancy in the literature that cold water marine fish oil given at a dose of 1ml per 4kg of body weight produces good results. Other oils or combination of oils have proven to be effective but there is no evidence of their superiority to fish oil. There is no evidence to support or disprove the notion that an Omega-6:Omega-3 ratio of 5-10:1 is optomal.
4. High levels of dietary LA , as found in many dog foods, do not produce the same results as supplementing with higher levels of GLA and EPA.

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5. There are no serious side effects to EFA supplementation in terms of wound healing, suseptability to infection or blood clotting.
6. There is no way of predicting the response of any atopic dog to EFA supplementation.
7. Essential poliunsaturated acids are of value in cancer management both as anti-inflammatory agents and as a non-carbohydrate energy source. The optimum dose is unclear but probably higher than for atopic dermatitis.
8. The optimium N3/N6 ratio in cancer therapy is unclear but high doses of EPA, as found in cold water marine fish oil, are of benefit.
9. In addtion to omerga-3 supplementation cancer patients, could benefit greatly from treatment with NSAIDs.
10. Poliunsaturated fatty acids undergo oxidation if improperly stored. Only high quality product should be used.
11. Further studies, in which the total dietary fatty acid content is controlled, are required.

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