



Articles of Interest

Essential Fatty Acid Therapy in Canine Atopic Dermatitis and Cancer

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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.

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.

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 omega-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 20:3:N6 and then can go one of two ways:

1. Further extra-cutaneous desaturation to arachidonic acid 20:4:N6 (**AA**)
2. Acted on by cyclo-oxygenase-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.

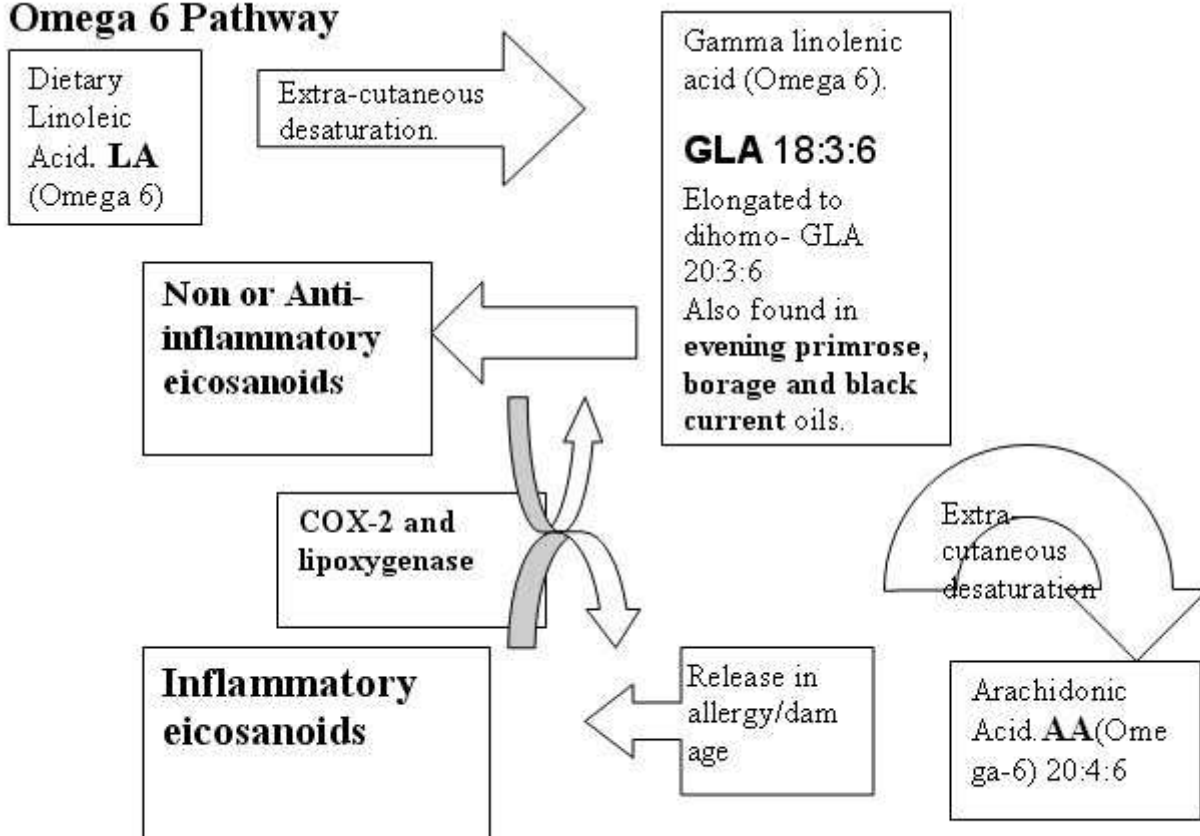
When COX-2 and LPO act on dihomogamma-linolenic acid (dihomo-GLA) a series of anti-inflammatory or less-inflammatory **eicosanoids** are produced. The anti-inflammatory effect of dihomogamma-GLA, is its ability to compete with AA for available COX-2 and LPO.

The Omega-3 Story

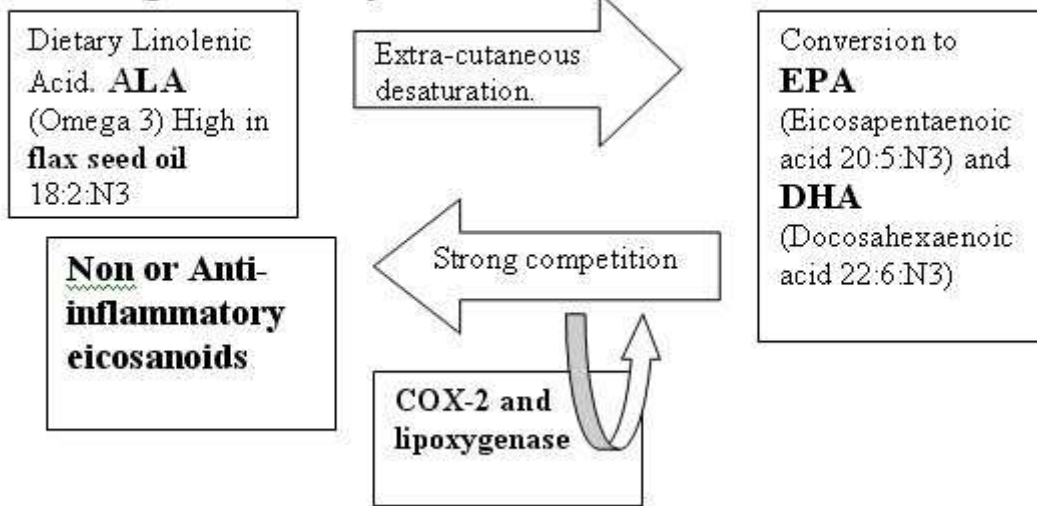
The most common source of omega-3 fatty acid is dietary alpha-linolenic acid (ALA). Remember this stuff is different to GLA, an omega-6 fatty acid. ALA is present in relatively small amounts in most dog food, including the premium brands. Flax seed oil is a rich source of ALA. ALA is desaturated to eicosapentaenoic 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 its EPA content.

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.

A. Omega 6 Pathway



Omega 3 Pathway



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

1. The dose of 40-50mg of EPA/kg/day (equivalent to 1ml of cold water marine fish oil per 4kg of body weight) is effective in reducing pruritis in canine atopic dermatitis. (4) .
2. 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)
3. There is a variability in the biochemical response between atopic dogs to fatty acid supplementation. (3) Dogs responding may represent a distinct biological subset (11).
4. There is a lag phase for the effect of polyunsaturated fatty acid therapy of between 4-12 weeks until maximal benefits are reached. (8)
5. Flax seed oil used for one month was no better than sunflower seed oil (LA source) (6) . Flax seed oil (ALA source) was as effective as fish oil when used for 10 weeks.(4)
6. 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)
7. There is no correlation between response to therapy and age, breed , sex , duration of disease or number of positive intradermal tests. (10)
8. Withdrawal of polyunsaturated fatty acid therapy and substitution with a control diet in dogs responding to N3-N6 therapy results in deterioration. (1) (11).
9. Evening primrose oil , a source of omega-6 GLA, is effective in reducing pruritis when compared to control dogs. (9)
10. Most dog foods supplemented with polyunsaturated 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 (approx N6:N3 ratio 17:1) was given to dogs fed a diet of 3.9% polyunsaturated fat but with 90% of these 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)

11. The response to fatty acid supplement must be separated out to the response to infection control in evaluating uncontrolled studies. (5)

Cancer

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

1. Non-steroidal anti-inflammatory drugs (NSAIDs) are proving of increasing, and possibly major, value in the management of cancer. Much of this work has been done in humans but translates to animals. There is now a vast literature on this topic. Piroxicam has been used to treat canine transitional cell bladder cancer. Its benefit probably is due to it being a NSAID and there is no evidence to support the use of this toxic drug over registered COX-2 specific NSAIDs. In humans many NSAIDs have been shown to be of benefit in a large number of cancers ⁴
2. Tumour cell cyclo-oxygenase-2 (COX-2) is induced in many cancers including canine squamous cell carcinomas ^{1 3}.
3. 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 ¹.
4. 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 omega-3, benefit cancer patients ².
5. The aim of the higher dose of omega-3 oil is competition 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.

Summary

- A. The dose of 40-50mg of EPA/kg/day (equivalent to 1ml of cold water marine fish oil per 4kg of body weight) is effective in reducing pruritis in a significant proportion of cases of canine atopic dermatitis
- B. 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.
- C. The time lag for benefits to reach maximum may be anywhere up to 12 weeks and no benefits may be seen for 8 weeks.
- D. 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.
- E. 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.
- F. There is no proven superior combination of oils. There is a consistency 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.
- G. There are no serious side effects to EFA supplementation in terms of wound healing, susceptibility to infection or blood clotting.

H. There is no way of predicting the response of any atopic dog to EFA supplementation.

I. Essential polyunsaturated 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.

J. The optimum N3/N6 ratio is unclear but high doses of EPA, as found in cold water marine fish oil, are of benefit.

K. In addition to omega-3 supplementation cancer patients could benefit greatly from treatment with NSAIDs.

L. Polyunsaturated fatty acids undergo oxidation if improperly stored. Only high quality product should be used. When using fish oil the EPO level should be 180mg/ml.

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