Tripping Lightly Down the Prostaglandin Pathways

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The mysterious and complex family of prostaglandins constitutes one of the most intriguing discoveries in the history of modern medicine. Discovered in 1936 by von Euler, prostaglandins derive their name from the fact that they were first detected in human seminal fluid. It was not until the advent of more sophisticated instruments 40 years later that these compounds could be studied in depth. Researchers discovered that the original substance is just one of a family of compounds found in every cell of the body; in fact, prostaglandins are found throughout the animal kingdom, even in species as lowly as insects, shellfish and corals.

Prostaglandins are a subset of a larger family of substances called eicosanoids. Other subgroups include thromboxanes, leukotrienes and lipoxins. Eicosanoids are localized tissue hormones that seem to be the fundamental regulating molecules in most forms of life. They do not travel in the blood like hormones, but are created in the cells to serve as catalysts for a large number of processes including the movement of calcium and other substances into and out of cells, dilation and contraction, inhibition and promotion of clotting, regulation of secretions including digestive juices and hormones, and control of fertility, cell division and growth. The list of biological functions involving prostaglandins is limited only by our ignorance of their effects. As research continues, so will our knowledge of these fascinating substances expand and grow.

Prostaglandins are produced in the cells by the action of enzymes on essential fatty acids. There are two prostaglandin pathways, one that begins with double-unsaturated omega-6 linoleic acid and one that begins with triple-unsaturated omega-3 alpha-linolenic acid. Both pathways essentially involve elongation of the 18-carbon EFA's to the 20-carbon root used in each of the three eicosanoid types, plus further desaturation. (See accompanying diagram.) On the omega-6 pathway, the Series 1 prostaglandins are produced from a 20-carbon, triple unsaturated fatty acid called dihomo-y-linolenic acid (DGLA) that is found in liver and other organ meats. The Series 2 prostaglandins are produced from a 20-carbon quadruple unsaturated fatty acid called arachidonic acid (AA) found in butter, animal fats, especially pork, organ meats, eggs and seaweed. On the omega-3 pathway, the Series 3 prostaglandins are procuded from a 20-carbon quintuple unsaturated fatty acid called eicosapentaenoic acid (EPA) found plentifully in fish liver oils and fish eggs.

Early research focused on the interplay between the Series 1 and Series 2 prostaglandins. In the most simple terms, the Series 2 prostaglandins seem to be involved in swelling, inflammation, clotting and dilation, while those of the Series 1 group have the opposite effect. This has led some writers, notably Barry Sears in his popular book The Zone, to call the Series 2 family the "bad" eicosanoids and to warn readers against eating liver and butter, sources of arachidonic acid, the Series 2 precursor. Sears also asserts that perfect balance of the various prostaglandin series can be achieved by following a diet in which protein, carbohydrate and fat are maintained in certain strict proportions. This is a highly simplistic view of the complex interactions on the prostaglandin pathway, one which does not take into account individual requirements for macro and micro nutrients, nor of imbalances that may be caused by nutritional deficiencies, environmental stress or genetic defects. Like all systems in the body, the many eicosanoids work together in an array of loops and feedback mechanisms of infinite complexity. Furthermore, liver and eggs are both highly nutritious foods. Liver supplies DGLA, a precursor of the Series 1 prostaglandins, and both liver and eggs supply DHA, an important nutrient for the brain and nervous system. Arachadonic acid found in butter and eggs is also an important constituent of cell membranes.

The Series 2 prostaglandins do indeed play a role in swelling and inflammation at sites of injury. This is not at all a "bad" effect, but an important protective mechanism--the body's way of immobilizing the affected site to prevent further injury and facilitate healing. Series 2 prostaglandins also seem to play a role in inducing birth, in regulating temperature, in lowering blood pressure, and in the regulation of platelet aggregation and

birth, in regulating temperature, in lowering blood pressure, and in the regulation of platelet aggregation and clotting.

Later investigators have focused on the balance between Series 2 and Series 3 prostaglandins. The Series 2 group is involved in intense actions, often in response to some emergency such as injury or stress; the Series 3 group has a modulating effect. Series 2 eicosanoids might be likened to the "fast lane" in that they are often associated "with an explosive, but transient burst of synthesis. . . if the rate of synthesis is too slow, there will be insufficient active eicosanoids to occupy receptors. If the rate is synthesis is too fast, excess active eicosanoids can cause pathophysiology." (1) The Series 3 prostaglandins are formed at a slower rate and work to attenuate excessive Series 2 production. Their response is "less vigorous." The omega-3 pathway might therefore be likened to the "slow lane." Adequate production of the Series 3 prostaglandins seems to protect against heart attack and stroke as well as certain inflammatory diseases like arthritis, lupus and asthma.

Research into prostaglandins holds enormous promise for the treatment of disease with various drugs that selectively inhibit or stimulate the production of specific prostaglandins. Such drugs might be likened to police officers used to direct traffic or called on to help at the scene of an accident. For most of us, however, the best way to ensure adequate prostaglandin production along with proper balance between the various series and their subsets is to follow a diet that provides precursors to eicosanoid production, and keeps the pathways free from blocks and potholes, a diet that provides fuel for our prostaglandin cars and keeps the highways clear.

One of the most common blocks in the prostaglandin chain involves delta-6 desaturase (D6D), the first sept in the production of prostaglandins from essential fatty acids. When action of this enzyme is blocked, so is the entire pathway. This vital enzyme is inhibited first and foremost by trans fatty acids found in margarine, shortening and hydrogenated fats.2 These should be avoided at all costs. In addition, excess omega-6 fatty acids from modern commercial vegetable oils inhibits the pathway that leads to the Series 3 group. This is because both pathways begin with desaturation by the same delta-6 desaturase enzymes. Too much omega-6 in the diet "uses up" the delta-6 desaturase enzymes needed for the omega-3 pathway.(3)

The modern diet contains large amounts of omega-6 fatty acids compared to that of a generation ago, because high omega-6 oils from soy, corn, cottonseed and safflower have been introduced into the food supply. They are used to make hydrogenated fats and as a replacement for traditional fats and oils such as olive oil, butter, coconut oil, goose fat and lard. The modern diet is also deficient in omega-3 fatty acids compared to that of a generation ago because modern farming methods have the effect of increasing the amounts of omega-6 and oleic acid in vegetables, fruits, fish, eggs, grains and legumes, while decreasing the amount of valuable triple unsaturated omega-3. A good way to put omega-3 fatty acids back into the diet is to add a small amount of flax oil, rich in linolenic acid, to salad dressing.

Deficiencies of biotin, vitamin E, protein, zinc, B12 and B6 all interfere with the action of delta-6 desaturase and other enzymes involved in prostaglandin production.(4) B12 is found only in animal foods. B6 is also found chiefly in animal foods. It is highly sensitive to heat. Best sources are raw dairy products, raw fish and raw meat. Zinc absorption is inhibited by phytic acid in whole grains and legumes, particularly soy, that have not been properly prepared. Best sources of zinc are animal foods--red meat, organ meats and some sea foods such as oysters. Alcohol consumption interferes with D6D, as does malnutrition and overeating--so moderation is the key to tripping lightly down the prostaglandin pathway. There is some evidence that an excess of oleic acid (found chiefly in olive oil and nuts) may inhibit prostaglandin production.(5) Even consumption of essential fatty acids should be restricted to about 4% of the diet. Excess of EFA's, especially omega-6 EFA's, can cause problems with both pathways. Excess consumption of sugar also interferes with the desaturating enzymes.

Diabetes, poor pituitary function and low thyroid function are synonymous with altered and inhibited D6D function.(6) These ailments are often treated with evening primrose, borage or black current oils, which contain GLA, the Series 1 precursor. Dietary GLA can be used when production is blocked by defective D6D

[illegible] action. Fish oils provide EPA and DHA, the production of which is also blocked by poor D6D function. Supplements of evening primrose, borage or black current oils, and of fish liver oils are a good idea for everyone.

Diseases caused by altered D6D function include diabetes, alcoholism, cancer, premature aging, high cholesterol, Crohn's disease, cirrhosis of the liver, eczema, PMS, noncancerous breast disease, Sjogren's syndrome, scleroderma, ulcerative colitis and irritable bowel syndrome. In cancerous cells, all D6D activity is lost. GLA (from evening primrose, borage or black current oils) inhibits the growth of cancer cells but not of normal cells. The effectiveness of GLA compared to most drugs in treating not only cancer, but all of the diseases caused by inhibited D6D function, may explain the Food and Drug Administration's efforts to suppress the sale of evening primrose oil and similar products.

Some popular writers claim that saturated fats in the diet inhibit the production of prostaglandins. Actually the reverse is true. Saturated fats in the diet improve the body's utilization of essential fatty acids,(7) and protect them from becoming rancid. Remember that the kind of fat the body itself makes is saturated fat, which it needs for energy and a variety of other purposes.

Lauric acid, a 12-carbon saturated fatty acid found chiefly in mother's milk and coconut oil, and in smaller amounts in butter, seems to improve the function of the omega-6 pathway.(8) When lauric acid is present in the diet, the long chain omega-6 fatty acids accumulate in the tissues where they belong, even when consumption of essential fatty acids is low. Unfortunately, highly useful and beneficial coconut oil has been forced out of the food supply by adverse propaganda originating with the fabricated food industry, which would rather use cheap hydrogenated oils rather than more expensive coconut oil for shortening.

The actions of delta-5 and delta-4 desaturase enzymes further along the pathway are less well understood, because they have not been as well studied. Nevertheless, it is known that diabetes, protein deficiency and alcohol all inhibit the action of D5D. Butter, eggs and organ meats provide arachadonic acid, the substrate for the Series 2 prostaglandins, and would be extremely important to include in the diet of diabetics and others whose D5D function may be compromised.

The desaturase enzyme systems do not work well in infants. This is why mammalian milk is rich in long chain fatty acids of both pathways--AA, EPA and DHA. DHA, the end product of the omega-3 pathway, is essential for the development and function of the brain. Egg yolk will be rich in DHA if the chickens are fed foods rich in omega-3 linolenic acid--flax meal, fish meal or insects. DHA-rich egg yolk fed to infants, beginning at about four months, is an easy way to ensure proper development of the brain, early speech, good coordination and freedom from learning disabilities. (The Japanese put a very high value on eggs as a brain food.) The desaturase enzyme systems also become less efficient in old age. Researchers at the University of California at Berkeley compared two groups of men in their eighties--those suffering from senility and those with all their mental faculties in tact. Their diets were similar with the exception of one item--the men with all their mental faculties intact ate at least one egg per day!(9) Vegans are deficient in the omega-3 fatty acids, particularly DHA.(10)

Carnivorous animals lack both D6D and D5D enzymes, and must obtain the longer chain fatty acids from their food supply. This is why carnivorous animals prefer organ meats to muscle meats, as these supply DGLA, AA and DHA. Some population groups that have been largely carnivorous for generations, such as the Eskimo and Irish seacoast peoples, also lack these enzymes. Fish liver oils and organ meats are a must for people with this kind of ancestry, otherwise their prostaglandin pathways are largely dysfunctional. Is this why certain groups so quickly degenerate into alcoholism and other chronic diseases when they no longer have access to sea foods and organ meats found traditionally in their diets?

In the 1930's, nutrition pioneer Weston A. Price studied primitive diets throughout the globe. He found that organ meats, butter, fish liver oils and fish eggs were highly valued items in every diet he studied.(11)

(Insects, high in superunsaturated fatty acids, are also highly valued among peoples who have little access to other animal foods.) He noted that all these foods were exceptionally rich in vitamins A and D. What he did not know was that these foods also supply long chain fatty acids the body needs to overcome any stumbling blocks that may lie on the prostaglandin pathways. Dr. Price was often called to the bedsides of dying individuals, when last rites were being administered. He brought with him two things--a bottle of cod liver oil and a bottle of high vitamin butter oil from cows eating growing grass. He put drops of both under the tongue of the patient--and more often that not the patient revived. He was puzzled by the fact that cod liver oil alone and butter oil alone seldom revived the dying patient--but the two together worked like magic.(12) Research into prostaglandins may supply the answer. High vitamin butter may be rich in AA and possibly other factors needed for the omega-6 pathway; and cod liver oil is rich in EPA needed for the omega-3 pathway. In addition, the saturated fatty acids in butter help the unsaturated fatty acids in cod liver oil to work more efficiently.

Many delicious traditional dishes provide the synergystic combination of LNA, EPA and DHA of the omega-3 family with AA of the omega-6 family and short and medium chain fatty acids--lox and cream cheese, caviar and sour cream, liver and bacon, salmon and Bernaise sause, dark green vegetables with butter, cream cheese and flax oil. In India, milk products provide AA and shorter chain fatty acids while insects provide the longer chain fatty acids of the omega-3 chain. Fish, pork and coconut oil provide all the necessary fatty acids in the Polynesian diet; American Indians valued fish, bear fat and oil of the eveining primrose plant. Traditional combinations of rich foods, therefore, need not be avoided. They provide factors that open both lanes of the prostaglandin pathway, creating a wide and open highway to skip along for renewed vitality and vibrant health.

Tips for Tripping Lightly Down the Prostaglandin Pathways

1. Avoid all hydrogenated fats
2. Avoid high levels of processed omega-6 vegetable oils, especially soy, corn, cottonseed and safflower oils
3. Use high quality butter
4. Use small amounts of flax oil in salad dressings.
5. Use coconut oil or whole coconut milk in cooking
6. Supplement with cod liver oil and evening primrose, borage or black current oils
7. Eat organ meats and fish eggs occasionally
8. Eat good quality eggs frequently
9. Eat raw meat or fish occasionally (Note: Fish should be marinated in an acidic medium, and meat should be frozen for at least 14 days before preparation, to avoid parasite contamination.)
10. Avoid high phytate foods that block zinc. These include grains, legumes and nuts that have not been properly prepared to reduce phytate content.13 Modern soy foods have potent zinc-blocking effects.
11. Avoid refined sweeteners like sugar and high fructose corn syrup
12. Eat and drink in moderation--but don't deprive yourself of delicious traditional foods.

Let's Get Technical ... About Prostaglandins

The omega-6 pathway begins with double-unsaturated linoleic acid (LA) found mainly in seed oils. It is desaturated by the action of a desaturating enzyme, delta-6 desaturase (D6D), resulting in an 18-carbon, triple-unsaturated fatty acid called gamma-linolenic acid, GLA. (GLA differs from the 18-carbon triple-unsaturated alpha-linolenic acid in that the unsaturated carbon double bonds are in different places along the carbon chain.) An elongase enzyme then adds two more carbon atoms to GLA, taking us another step along the prostaglandin pathway to form a 20-carbon triple-unsaturated fatty acid called dihomo-gamma-linolenic acid (DGLA). DGLA forms the root of the Series 1 prostaglandins such as PGE1, PGF1a, and PGD1, and thromboxanes such as TXA1

DGLA is then transformed into 20-carbon quadruple-unsaturated arachidonic acid (AA), which is the root or

DGLA is then transformed into 20-carbon quadruple-unsaturated arachidonic acid (AA), which is the root or precursor of the Series 2 eicosanoids. The Series 2 family includes a number of prostaglandins such as pge2 pgf2a and pgd2 ,prostacyclins such as pgI2, thromboxanes such as TXA2, leukotrienes and lipoxins.

Series 3 prostaglandins are produced on another pathway entirely, one that begins with triple unsaturated alpha-linolenic acid, found in seed oils of northern origin, like flax. This essential fatty acid is desaturated twice and elongated once to produce eicosapentaenoic acid (EPA), a 20-carbon fatty acid with five double bonds. EPA is the root substance of the Series 3 family that includes the prostaglandins such as PGE3, PGH3 and PGI3, thromboxanes such as TXA3 and leukotrienes. EPA is then further elongated and desaturated to produce docosahexaeonic acid (DHA) a 22-carbon fatty acid with six double bonds. DHA is found plentifully in the brain and is in fact essential for the development and function of the brain. DHA also acts as a storage molecule. It can be shortened and resaturated to produce EPA and the Series 3 eicosanoids.

During the early years of prostaglandin study, the eminent researcher David Horrobin described the complex relationships between thromboxanes and prostacyclins of Series 2 (TXA2 and PGI2) with prostaglandins PGE1 of Series 1.14 For example, TXA2 seems to be essential for the release of calcium from the cells, while PGI2 inhibits release of calcium. At low concentrations PGE1 blocks the effects of PGI2 and enhances those of TXA2; at higher concentrations it imitates PGI2 and blocks TXA2 . He notes that a variety of diseases can be explained in terms of imbalance between Series 1 and Series 2 prostaglandins. Over-synthesis of Series 2 prostaglandins encourages thrombosis; inhibition of overall prostaglandin syntheses can elevate blood pressure, and paradoxically, increase serum cholesterol. Kidney disease as well as hyperthyroidism are associated with inadequate amounts of PGE1. TXA2 synthesis seems to be deficient in cases of ulcerative colitis, leaving to an overproduction of other prostaglandins. Massive overproduction of certain prostaglandins seems to be involved in rheumatoid arthritis. A failure of TXA2 production, with concurrent excess production of other prostaglandins, leads to an increased susceptibility to cell mutation and hence to cancer. PGE1 deficiency seems to be involved in psoriasis and schizophrenia. On the other hand, manic behavior is associated with higher PGE1 production rates than normal. Depression is associated with elevation of TXA2 synthesis. Various types of muscular dystrophy are associated with accumulation of calcium in the cells, due to reduced TXA2 production. Deficient TXA2 formation may also be involved in multiple sclerosis. Migraine headaches with accompanying gastrointestinal disturbances can be explained by increased prostaglandin production, particularly PGE1.

The action of many drugs can be explained by their ability to stimulate or interfere with Series 1 and Series 2 prostaglandin production. Aspirin and steroids inhibit TXA2 activity and therefore reduce swelling; Lithium inhibits PGE1 which seems to be elevated in manic-depressive disorders. Melatonin, amantadine and colchicine (used to treat gout) activate TXA2 .

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