



Is Fish-Oil an “All-Powerful“ Active Substance?

A broad spectrum of action is indicated

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Please note that n-3 and n-6 fatty acids are nowadays commonly referred to as omega-3 and omega-6 fatty acids.

Introduction

The action of n-3 fatty acids from fish oil in the treatment of a wide variety of illnesses has been described and substantiated in several articles published in SANUM-Post. May one draw the conclusion from such articles that fish oil is some kind of “miracle drug”? Since the earliest days of medicine such “miracle drugs” have appeared over and over again, although on closer examination their efficacy could not be established.

Various active substances again and again have been found to have new effects which put the originally discovered ones in the shade. One such substance is Acetylsalicylic acid. Originally this was developed as an anti-rheumatic/antiphlogistic agent. Later its anticoagulant function was discovered, and later still its action as a prophylactic for cancer of the colon. It turned out that all these functions operated via the influence of mediators, particularly the inhibition of prostaglandin synthesis. Thus its broad spectrum of action may be attributed to one common pharmacological principle. In the case of the n-3 fatty acids we encounter an analogous situation.

One aim of this review is to demonstrate, by means of the metabolism of n-3 fatty acids, which changes in mediatory patterns lead to corresponding therapeutic effects. Of course, in so doing we

must take into account the fact that research in these areas is ongoing, so that we can only speak in terms of a state-of-the-art snapshot.

It is an essential aim of all scientific research to trace individual results back to superior principles, to allocate them a place within these principles and thus to explain them. In finding an explanation for the many actions of n-3 fatty acids, this procedure also turned out to be fruitful, and led to a plausible theory which explained a great deal.

Since the beginning of evolution, fatty acids have played a central role as components in the structure of biological membranes. As membranes developed, biological systems succeeded in developing an individuality for the first time. At a later stage, all communication processes between certain cells had necessarily to take place via membrane changes. Thus we should not be surprised that adapted membrane building blocks developed into the most important of mediators.

Thus, whether we are discussing the way in which prostaglandins or leucotrienes work, or the metabolism of lipoproteins in connection with the proper development of the membrane system of the human brain, a decisive role is always played by the fatty acid pattern of the diet, as the fund of source material. The polyunsaturated fatty acids are indispensable building blocks of important, biologically active substances, of the tissue hormones or mediators, and of the actual structures of the membranes.

Structural features and metabolism of n-3 fatty acids

The n-3 fatty acids are distinguished by cis-double bonds, beginning at the third carbon atom, counting from the methyl end of the molecule (Linolenic acid type). They differ from the n-6 fatty acids, in which the bonds begin at the sixth carbon atom of the chain (Linoleic acid type).

Unlike plants, animal organisms are not capable of constructing these specific basic structures or of converting them into each other. Therefore these two types of fatty acids must be regarded as two strictly separate groups. However, in every organism there exists the possibility of a chain extension, including the introduction of further double bonds.

As shown in Figure 1, the higher links of both classes of substance can be constructed enzymatically by means of alternating desaturation and elongation. However, new double bonds can only be introduced towards the carboxyl end of the molecule. Extension of the chain also takes place only in the carboxyl direction. Dehydration occurs between the 6th and 7th carbon atoms of the C-18 bonds, between the 5th and 6th carbon atoms of the C-20 acids and the 4th and 5th carbon atoms of the C-22 acids, and is an expression of the activity of Delta-6, Delta-5 and Delta-4 desaturases.

Clearly, in the course of evolution, a partial specialisation has taken place in the fatty acid patterns of plants so far as the synthesis of

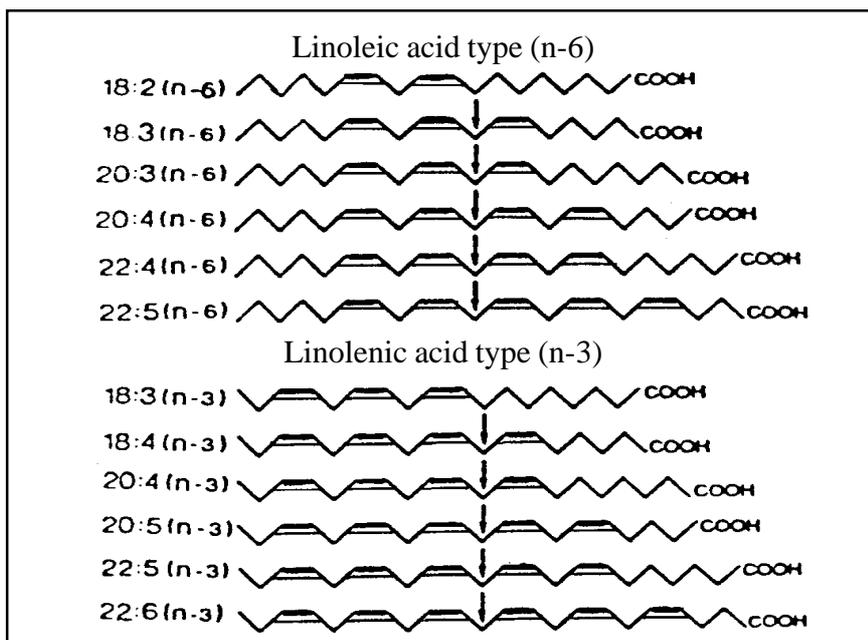


Figure 1: Fatty acids of the Linoleic acid type (n-6) and of the Linolenic acid type (n-3) and the products resulting from their dehydration and chain extension.

polyunsaturated fatty acids is concerned. Whereas a significantly higher proportion of n-3 fatty acids is present in the evolutionarily older algae, e.g. phytoplanktons, mosses and ferns, meaning that the n-3/n-6 relationship is more “equal“, the higher flowering plants (maize, sunflowers, soya and wheat) generally show a preference for the n-6 fatty acids (Linoleic acid 18:2 (n-6)), although even here there are also oils with a markedly higher proportion of n-3 fatty acids, e.g. of Linolenic acid 18:3 (n-3), such as rapeseed oil and linseed oil.

The n-3 fatty acids of phytoplankton (algae) form the basis of the nutritional chain of fish. As a result of dehydration and/or chain extension, further fatty acids are formed from them. Here the longer links of the n-3 fatty acids predominate: Eicosapentaenoic acid 20:5 (n-3), Docosapentaenoic acid 22:5 (n-3) and Docosahexaenoic acid 22:6 (n-3).

Theoretically one might be tempted to replace these long-chain n-3 fatty acids with shorter n-3 fatty acids of plant origin. However, experimental results show that the conversion of Linolenic acid into Eicosapentaenoic acid (EPA) proceeds so slowly that very large quantities of the latter fatty acid, about ten times the quantity of the other, would need to be taken, in order to achieve the same therapeutic effect. These unacceptably large quantities make the use of linseed oil in therapy impossible, for reasons of compliance.

How n-3 fatty acids act

The pharmacological action of n-3 fatty acids will be explained below by means of a comparison with the action of genuine drugs:

As shown in Figure 2, antiphlogistics have an inhibiting action on prostaglandin synthesis. Whereas glucocorticoids inhibit phospholipase A₂, thus intervening at an early stage of events, non-steroidal

antiphlogistics (e.g. ASA) block the cyclooxygenase system, by which Arachidonic acid and other unsaturated C20 acids, the so-called eicosaenoic acids (from eicosa or icos = Greek: twenty) are transformed into cyclic endoperoxides. From eicosaenoic acids for instance, prostaglandins, thromboxanes, leucotrienes, hydroxy fatty acids and lipoxins are synthesized, and these are included under the overall heading of eicosanoids. (Fig. 2)

Eicosanoids such as these are formed almost everywhere in the body from fatty acids released locally from membranes. Even in tiny concentrations they are biologically highly effective. They must be constantly synthesized, because they cannot be stored. They include the prostaglandins, the prostacyclins and the thromboxanes. All mediators have a modulating action on numerous functions - from allergy and athero-genesis, via thrombogenesis to cell proliferation. Prostaglandins are mediators which stimulate inflammatory processes, pain sensation and feverish manifestations.

These disadvantageous effects may be prevented, not only by the already mentioned medicines such as corticosteroids and prostaglandin synthetase inhibitors, but also by eliminating Arachidonic acid (C20:4 n-6) from the enzyme systems by means of analogue fatty acids, e.g. EPA (C20:5 n-3). In this way, using the same mechanisms, other mediators are created from the n-3 fatty acids, having less aggressive properties than those which originated from n-6 acids. This is summarised in Figure 3.

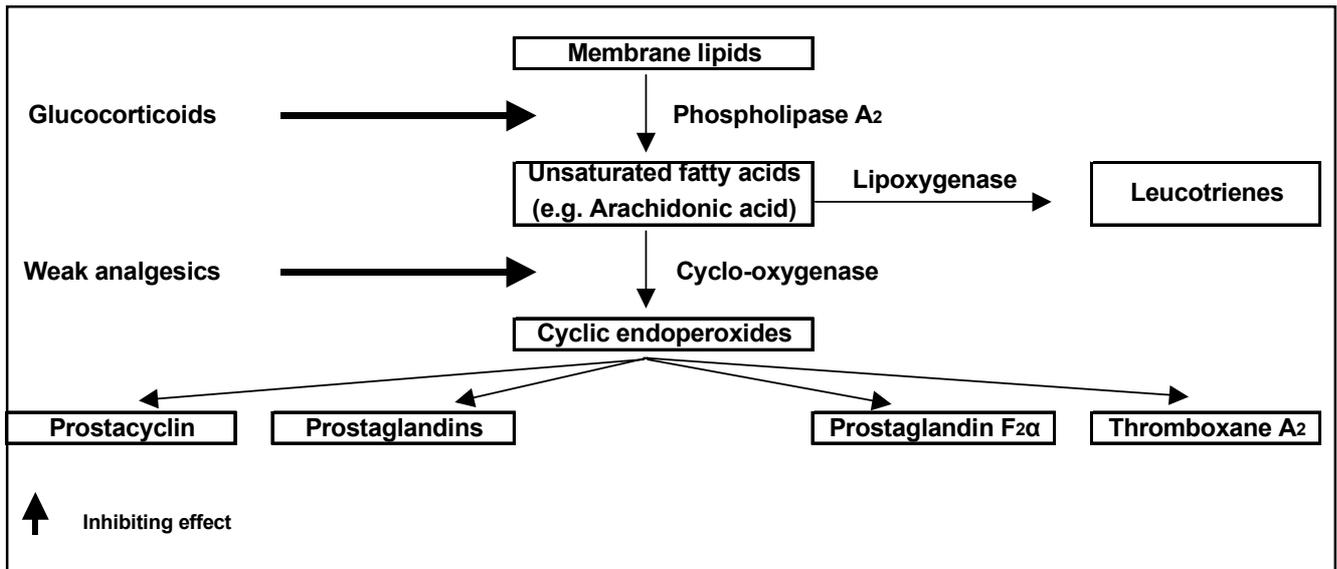


Figure 2

In the absence of a supply of EPA the cyclic peroxides of Arachidonic acid are formed, and from them the mediators shown in Figure 3, such as the inflammatory prostaglandins PGE₂ and PGF_{2α} and (in the thrombocytes) the aggregatory TXA₂, which causes vasoconstriction. Instead of these problematic mediators, following an increase in the supply of n-3 fatty acids, particularly EPA, the less inflammatory prostaglandins PGE₃ and PGF_{3α} are formed. By analogy, Thromboxane TXA₃, which is less aggregatory, and PGI₃, which is a stronger inhibitor of aggregation than PGI₂, are also created.

As may likewise be seen from Figure 3, Arachidonic acid can be converted into the leucotrienes LTB₄ and LTC₄ by means of a further enzyme system, known as the Lipoxygenase pathway (Figure 2). These are also extremely effective mediators of inflammation. This pathway is not influenced by prostaglandin synthetase inhibitors. However, a supply of EPA means that fewer leucotrienes LTB₄ and LTC₄ are produced, being replaced

by the less active leucotrienes LTB₅ and LTC₅.

Thus, by supplying EPA, it is possible to make critical changes to the whole mediatory spectrum in such a way that those mediators which reinforce illness are driven back and the formation of eicosanides, which favour health, is promoted. By reason of the connections described above, it seems quite astonishing at first sight that the formation of problematic mediators is apparently the “normal” state of affairs.

However, there is a very plausible theory which explains this phenomenon: there is evidence that our early ancestors lived on a low-fat diet, and that the fatty portion of their diet was relatively rich in n-3 fatty acids. There are many indications that their living space also included large stretches of water. This is supported, apart from our affinity for water, which is still strong, by our markedly reduced covering of body-hair and, above all, by our ability to regulate our breathing voluntarily, which is a prerequisite for swimming and

diving. This is possibly also the basis for the development of a differentiated language.

During this relatively lengthy period of evolution, human metabolism is likely to have adapted to an appropriate diet relatively rich in n-3 fatty acids. The beginning of agriculture marked a fundamental shift in our diet towards cereal products, with their high proportion of plant-derived n-6 fatty acids. Since that time our diet has no longer satisfied the original requirements which, however, still form the basis of our metabolism.

Because of the predominance of n-6 fatty acids in our “modern diet”, the n-6 eicosanoids from Arachidonic acid hold sway, among them - in the thrombocytes - Thromboxane TXA₂, which promotes aggregation and is vasoconstrictive; in the vascular endothelium its antagonist, the vasodilative Prostacyclin (PGI₂); in the granulocytes, monocytes and macrophages the leucotriene LTD₄, which is chemotactic and promotes inflammation.

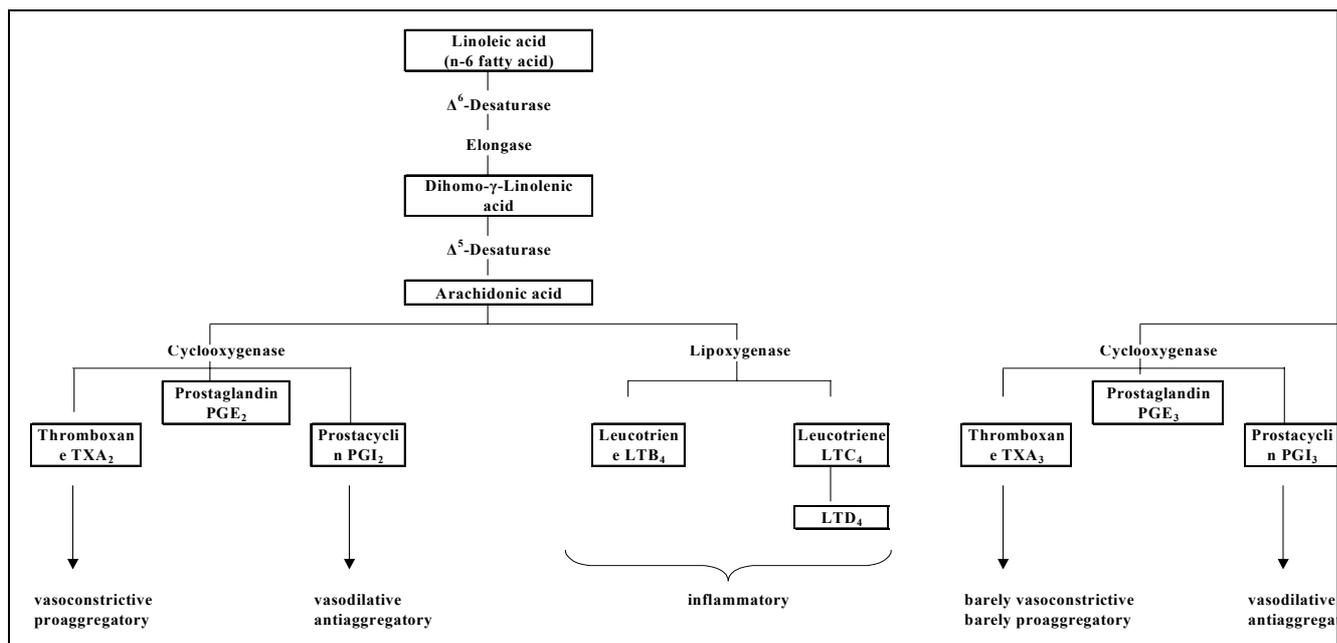


Figure 3: Metabolic paths of Eicosanoids of the n-3 and n-6 families.

Their substances of origin, the n-6 fatty acids, are found especially in wheatgerm, vegetable oils and so-called “diet margarines“. Because of the vasodilative prostacyclin (PGI_2) - the only positive effect (which is also exhibited, and to a larger extent, by PGI_3 , derived from EPA) - these plant fats are considered “particularly healthy“.

Considered in the context of a balanced intake of essential fatty acids, we once again see the truth of the saying: “We are what we eat“. It is the best way of typifying the situation here. Incidentally, the principle of combatting pathogenic changes by a change of diet is already practised by chimpanzees.

General action of n-3 fatty acids on membranes

Each membrane consists of a phospholipid bilayer (Figure 4), in which cholesterol, sphin-gomyelins, proteins, glycoproteins and other structural elements are stored. The lipid bilayer is normally formed of lipophil remains of various types of

fatty acids. The hydrophil remains delineate the membrane on both the inside and the outside of the cell.

The state of the lipid phase resembles a viscous fluid and determines the mechanical properties and the fluidity of the corresponding membranes. Basically it depends on the length of the chain, and on the number and arrangement of the double bonds of the fatty acids which make up the lipid bilayer. Since the n-3 and n-6 fatty acids differ radically in their structure, this also affects the properties of the membrane.

Thus an elevated n-3 fatty acid content results *inter alia* in a greater fluidity of the membrane. In red blood corpuscles this results in a greater propensity for deformity. This assists the passage of erythrocytes through narrow vessels, resulting in an improved blood-flow; this is expressed in reduced viscosity of the blood [2]. This could have therapeutic consequences for diabetics: following n-3 fatty acid intake they

have likewise exhibited elevated fluidity of membranes. This resulted in an improvement in transport activity, permeability and other important functions of the membranes.

The brain contains a particularly large number of membrane lipids. Thus we can easily appreciate that a balanced supply of all available fatty acids is of special importance here if development is not to be disordered. For the growth spurt in the central nervous system between the 24th and 40th weeks of pregnancy (during this time there is a weight gain from 75 to 400 grams [12]) the foetus requires as diverse a selection as possible of long-chain polyunsaturated fatty acids, in order to synthesize structural and functional lipids, which need to be made available by the maternal organism via the placenta.

In premature babies, who usually have no adequate endogenous synthesis of these fatty acids at their disposal, the concentration of Arachidonic and Docosa-

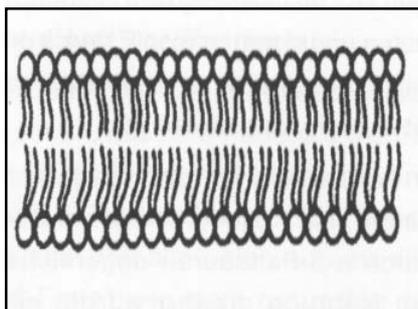


Figure 4: Bilayer membrane.

hexaenoic acids in the plasma and brain tissue decreases rapidly if they are not breastfed and are given commercial milk formula preparations instead. In such cases the result may well be functional impairment, particularly of the psychomotor and visual development. However, one relevant interventional study showed that supplementing the milk formula with fish oil or Docosa-hexaenoic acid can bring about a normalisation of the fatty acid status and mental development.

At the age of one year the children of the collective, which was fed a diet enriched with n-3 fatty acids, exhibited a clearly improved learning ability. The visual acuity of these children was also better in comparison with the control group, and correlated with the Docosahexaenoic acid level. Also, since 1991 it has been officially recommended that infant milk for premature babies should be enriched with these essential, long-chain fatty acids [12].

Derivation of the various actions on the basis of biochemical effects

On the basis of these principles many of the “actions“ of a diet rich in fish oil can be explained. The treatment of inflammatory illnesses

is based on this diminished formation of mediators which favour inflammation, as described above.

Fish oil as an adjunctive therapy in the treatment of psoriasis

Epidemiological investigations have shown that psoriasis occurs twenty times more frequently in Europeans than in Eskimos [11, 13]. In the latter, the proportion of n-3 to n-6 fatty acids shows a preponderance of n-3. This is reflected in the composition of the blood and tissue lipids.

In psoriatic foci the concentration of Arachidonic acid and that of the mediators derived from it is strongly elevated [3]. Enzyme preparations from psoriatic tissue exhibit an intensified synthesis of 12-HETE and LTB_4 from Arachidonic acid [6]. Taking fish oil for two months results in a competitive reduction in lipoxygenation of Arachidonic acid.

Vice versa, intracutaneous injections of 5-Lipoxygenase products (LTB_4 , LTC_4 , LTD_4 and LTE_4) in normal skin result in inflammatory reactions, such as erythema and infiltration by neutrophil leucocytes [21]. Local applications of LTB_4 on normal skin, in concentrations that have been demonstrated in psoriatic foci, resulted in intraepidermal micro-abscesses, which resembled those found in characteristic histological psoriasis specimens [3].

Substances that block the cyclooxygenase route which competes for the Arachidonic acid substrate must augment the quantity of mediators favouring inflammation which are formed via the

lipoxygenase route (Figure 3). This leads to an aggravation of the psoriasis symptoms, if only n-6 fatty acids are consumed. In fact, patients who were simultaneously treated with Indomethazin, which inhibits cyclooxygenase, an aggravation of the illness was observed. Thus the pathogenesis and treatment of psoriasis may be informally explained on this basis. As has been shown in numerous clinical studies, fish oil may be used to complement established treatments for psoriasis. Obviously the inflammatory elements of psoriasis are inhibited.

Treatment of rheumatic diseases

Increased intake of EPA(20:5 n-6) in fish oil results in the fatty acid displacing Arachidonic acid (20:4 n-6) as the “normal“ substrate of the bonding centre of cyclooxygenase and 5-lipoxygenase. Consequently, taking fish oil inhibits the formation of aggressive prosta-glandins, which favour inflammation, and also of the mediator LTB_4 from Arachidonic acid. At the same time, in the competitive reaction, fewer aggressive prostaglandins and less of the leucotriene LTB_5 are formed from EPA. This results in a lower concentration of LTB_4 in the peripheral blood [9].

The leucotriene LTB_5 , formed from EPA, has much slighter chemotactic properties, and consequently has much less of a pro-inflammatory action [22]. Furthermore, n-3 fatty acids are capable of lowering the concentration of free radicals in activated granulocytes [24].

The action of fish oil on rheumatic diseases, as demonstrated in clinical

studies, may be attributed to these effects. In the meantime a further mechanism of action has been elucidated: interleukins are locally acting protein hormones, which stimulate proliferation. Interleukin-1, for instance, is formed by macrophages and not only stimulates T-lymphocytes, but also activates other effector cells. This co-ordinated reaction of the organism is called an "acute phase response" and, *inter alia*, it effects an increase in the biosynthesis of about 30 plasma proteins in the liver. This results, *inter alia*, in a raised ESR.

Efficacy in chronic inflammatory diseases of the intestines

Following a randomised, double-blind, placebo-controlled multicentre study of 24 patients, success has also been reported in the treatment of ulcerative colitis with fish oil. In all the patients the disease manifested with diarrhoea and signs of rectal inflammation. As well as treatment with Prednisone and Sulfasalazine, the patients were given fish oil capsules (3, 24g Eicosapentaenoic acid + 2,14g Docosahexaenoic acid). The crossover study covered two treatment periods of four months (fish oil and placebo), which were separated by a one-month wash-out period. The following criteria were tested: general symptoms; sigmoidoscopy with rectal biopsy; prostaglandin-E₂ and Leucotriene-B₄ levels in the rectal dialysate.

After four months of treatment with fish oil, the results showed significant lowering of the levels of Leucotriene-B₄ in the rectal dialysate, a significant improvement of the histological index, both acute and

overall, and a significant weight-gain, whereas in the placebo phase none of these variables showed any significant change. In the patients simultaneously treated with Prednisone it was possible to reduce the Prednisone dosage during the fish oil phase on average from 12.9 to 6.1 mg daily; during the placebo phase, on the other hand, it had to be increased from 10.4 to 12.9 mg daily [23]. In the treatment of Crohn's disease too there have been correspondingly promising results [1].

Indirect effects from using different eicosanoid samples

A delay in the development of cancer of the colon may be regarded as an indirect effect for, in the meantime, it seems to have emerged that n-3 fatty acids are also capable of delaying the proliferation of degenerate cells [4,15]. The starting point for fundamental investigations was the observation that patients who for many years had been taking regular doses of antiphlogistics which inhibit the production of prostaglandinsynthetase - maybe as part of a course of treatment for rheumatism - developed cancer of the colon only half as frequently as the normal population.

New findings regarding the function of cyclooxygenase explain the tumour-inhibiting action which had been observed. Medicines such as Acetylsalicylic acid and other nonsteroidal antirheumatics have an antiinflammatory action because they are cyclooxygenase inhibitors. Thus they suppress the activity of the enzyme which promotes the degeneration in colonic polyps. Since then there has been success in elucidating the molecular

processes involved in cell degeneration with regard to hereditary predisposition to cancer of the colon.

It is well-known that, in patients who have a familial predisposition to adenomatous polyposis (FAP), which manifests in numerous initially benign growths on the intestinal wall, over the years some of these polypi first grow more rapidly and finally degenerate into carcinomas. In these patients the APC gene (adenomatous polyposis coli) is mutilated. This DNA damage admittedly does not necessarily result in cell degeneration; however, from a statistical point of view these patients contract colonic cancer far more frequently than the normal population. If, in one of these polyp cells, the second allele of the diploid cell nucleus is also destroyed as a result of (chance) mutation, then this gene also ceases to function, and so the degeneration of the cell commences. In the emergence of all forms of cancer of the colon similar processes occur; even if this happens to a lesser extent, the principle is the same.

In animal experiments it has now been possible to demonstrate [6, 14] that one of the first changes in the polyps when still benign consists in an intensification of the biosynthesis of the enzyme cyclooxygenase-2 (Cox-2), which is involved in prostaglandin synthesis. This enzyme acts as a catalyst in the second stage of conversion of Arachidonic acid into prostaglandins (*see Figure 3*). Japanese scientists [14] succeeded in breeding mice, in which not only was one of the two APC genes mutilated, but also the inherited



predisposition to cyclooxygenase-2. Thus, in homozygous specimens with the latter gene defect, a normal protein biosynthesis of cyclooxygenase-2 was no longer possible.

As a consequence of the missing cyclooxygenase-2 gene and the resultant lack of the enzyme itself, surprisingly the number of intestinal polypi noticeably declined. Furthermore the growths of the benign polypi were much less pronounced, and the polypi remained smaller. The same antitumoral effect could also be achieved in animals with genes intact when the activity of the cyclooxygenase enzyme was inhibited with doses of the appropriate inhibitor. This provided proof of the causal relationship between cyclooxygenase-2 activity and aggressive mediators on the one hand and tumor growth on the other hand.

Opportunities for employment of fish oil in gynaecology

It is clear that the efficacy of fish oils in the treatment of dysmenorrhœic complaints is based on changes in the eicosanoid profile. A starting point is the fact that prostaglandins derived from n-3 fatty acids have a stronger vasodilative, but a weaker vasoconstrictive action than those synthesized from n-6 fatty acids.

Initially these assumptions were purely theoretical; however, they appear to be confirmed in clinical investigations: As a result of a fish-rich diet, not only was there an improvement in the clinical complaints of patients with severe and treatment-resistant dysmenorrhœa, but under this treatment the abnormal prostaglandin levels and relationships in the menstrual blood became normal.

The process of childbirth too is triggered by prostaglandins, among other factors. It has been demonstrated in clinical studies that the time of birth can be delayed by modifying the prostaglandin pattern by means of fish oil. Therefore supplementation with fish oil, especially in the third trimester of pregnancy, represents an efficacious, cost-effective and comfortable treatment method for combatting premature births.

Opportunities for use in nephrology

It has now been established that chronic inflammatory renal diseases may also be favourably influenced by fish oil. In patients with IgA nephropathy, fish oil can help to slow down the decline in renal function, as shown in a study conducted at the Mayo Clinic [5].

Effects on atherosclerotic changes

A clinical investigation was carried out, with a total of 31 randomised controlled studies on 1356 patients, on the lowering of blood pressure by means of n-3 fatty acids [25]. Overall a significant lowering of blood pressure was established, although the results of the different studies showed a high degree of variation. Healthy subjects showed no appreciable change in their blood pressure from taking fish oil. On the other hand, in 415 patients with arterial hypertension the blood pressure was significantly lowered. A lowering of blood pressure was also recorded in groups of patients suffering from hypercholesteræmia, coronary heart disease and diabetes mellitus as their primary diagnosis

as a result of a course of fish oil treatment, although the change was not significant.

Altogether a clear relationship between dosage and effect was observed, for both systolic and diastolic blood pressure. It is certain that the mechanism for lowering of blood pressure is multifactorial. Here too the modification of the pattern of numerous tissue hormones and enzymes has a part to play. Thus it has been shown that n-3 fatty acids in tissue cultures inhibit a protein (PDGF α), which is normally formed by the endothelium and promotes the proliferation of unstriped vascular muscle cells [8]. Since these processes of proliferation play a key role in atherogenesis, this effect may well assume major significance.

As can be seen from Figure 3, more thromboxanes A₂ are formed under treatment with fish oil. Since the mutual relationship between thromboxanes A₂ and A₃ has a critical influence on blood coagulation, it is possible to explain a favourable protracted bleeding time on this basis. In the early Middle Ages the Vikings carried out raids as far away as Greenland. When they got involved in skirmishes with the Eskimos, they noticed that Eskimos, even after death, continued to bleed for a long time. Since then this phenomenon has been confirmed: Eskimos bleed for almost double the normal length of time [7]. This is the consequence of their altered fatty acid composition in the phospholipids of the thrombocytes, with a greater proportion of n-3 fatty acids and a lesser proportion of n-6 fatty acids.



In healthy subjects, following a daily intake of 10g fish oil over four weeks, a significant increase of 15% in the bleeding time was observed.

A lowering of the serum triglyceride level by fish oil has been demonstrated in patients with various forms of hypertriglyceridemia [10, 16-20]. This was dosage-dependant, and there was a negative correlation with the initial reading. Lowerings of the triglyceride level are always an expression of a decrease in the VLDL fraction. The effects on HDL and LDL are only slight and demonstrate the close metabolic relationship with the VLDL fraction. As usual, HDL-cholesterol reflects a mirrorimage of the triglyceride level. It has an obvious correlation with the interaction between lipids and the corresponding lipoproteins which transport them, and may be regarded as a further independent action of n-3 fatty acids.

The formation of atherosclerosis is a complex event and consists of

- elevated blood pressure,
- altered lipoprotein pattern,
- coagulatory disorders,
- endothelial damage of inflammatory origin.

It has already been shown that the first three of these causes may be favourably influenced by fish oil. Inflammatory damage to the endothelium, possibly of bacterial origin, has been increasingly discussed in recent times. This too can be halted as a result of changes in the eicosanoid pattern. To this must be added the delay of boosting effects: in the vascular wall, especially those of the small arteries

and arterioles, Prostacyclin (PGI₂) is formed. Its action opposes that of TXA₂ and is anti-aggregatory and vasodilative. In healthy people its action outweighs that of its antagonist TXA₂.

In cases of damage to the endothelium (=injury) there is a severe reduction in the formation of PGI₂, which results in wound closure. Interestingly, in patients with arteriosclerosis the formation of PGI₂ is generally depressed. This fact is under discussion as an important pathogenic factor. It can be favourably influenced by fish oil.

Thus altogether it appears that the treatment and prevention of cardiovascular disease is decidedly more effective with n-3 fatty acids than with n-6 fatty acids. The former are more effective because they favour neither aggregation nor inflammatory processes and, moreover, they have only a weak chemotactic action.

Résumé

So it appears that fish oil not only supplies essential fatty acids, but also has a mild pharmacological action. In the space available it has only been possible to describe its most important and best substantiated actions. However, it should be mentioned that discussions are also taking place regarding its action in diabetes, in certain forms of bronchial asthma, and in multiple sclerosis.

Thus fish oil is not so much an allpowerful active substance as an essential part of our diet, and an insufficient supply of it favours the onset of a plethora of illnesses. *Vice*

versa, fish oil preparations represent a complementary treatment for many illnesses. We may eagerly await further scientific results in this area.

Literature

- (1) Beluzzi, A., et al.: *New Engl. J. Med.* 334: 1557-1560 (1996).
- (2) Bertsch, S.; Zakaria, B.: *ngm*: 389-393 (1989).
- (3) Brain, S.; Camp, R.; Derm, F.F.; Drowd, P.; Black, A.K.; Graeves, M.: *The release of leucotriene B4-like material in biologically active amounts from the lesional skin of patients with psoriasis. J. Invest. Dermatol.* 83: 70-73 (1984).
- (4) Bueno-de-Mesquita, H.B.: *Highlights of the International conference on food factors (ICoFF): chemistry and prevention. Hamamatsu, Japan. Eur. J. Cancer Prev.* 5: 209-215 (1995).
- (5) Donadio, J., et al.: *N. Engl. J. Med.* 331: 1194 (1994).
- (6) DuBois, R.: *Gastroenterology* 111: 1134.
- (7) Dyerberg, J.; Bang, H.O.: *Haemostatic function and platelet polyunsaturated fatty acids in Eskimos. Lancet II*: 433-435 (1979).
- (8) Fox, P.; DiCorleto, P.: *Science* 241: 453 (1988).
- (9) Goetzl, E.J.; Wong, M.Y.S.; Payan, D.G., et al.: *Effects of eicosapentaenoic acid on immune responses and inflammation in humans. In: Simopoulos, A.P., et al.: Health effects of polyunsaturated fatty acids in seafoods. Academic Press, Orlando, 239-246 (1986).*
- (10) Hamazaki, T.R., et al.: *Effects of fish oil rich in eicosapentaenoic acid on serum lipid in hyperlipidemic hemodialysis patients. Kidney Int.* 26: 81 (1984).
- (11) Horrobin, D.F.: *Low prevalence of coronary heart disease, psoriasis, asthma and rheumatoid arthritis in Eskimos: are they caused by high dietary intake of eicosapentaenoic acid, a genetic Variation of essential fatty acid metabolism or a combination of both? Med. Hypotheses* 22: 421-428 (1987).
- (12) Koletzko, B.: *Bericht über den ersten europäischen Pädiatriekongress. Paris 1994. ÄZ* 46: 16 (1994).
- (13) Kronmann, N.; Green, A.: *Epidemiological studies in the Upnervik*



- district Greenland. *Acta Med. Scand.* 208: 401-406 (1980).
- (14) Masanobu, O.: *Cell* 87: 804.
- (15) Noguchi, M.; Rose, D.P.; Earashi, M.; Miyazaki, I.: *The role of fatty acids and eicosanoid synthesis inhibitors in breast carcinoma. Oncology (Basel)* 52: 265-271 (1995).
- (16) Phillipson, B.E., et al.: *Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia. New Engl. J. Med.* 312: 1210-1216 (1985).
- (17) Rogers, S., et al.: *Effects of fish oil supplement on serum lipids, blood pressure, bleeding time, hemostatic and rheological variables. Atherosclerosis* 63: 137-143 (1987).
- (18) Rylance, P.B., et al.: *Fish Oil Improves Lipids and Reduces Platelet Aggregation in Haemodialysis Patients. Nephron* 43: 196-202 (1986).
- (19) Saynor, R.; Verel, D.; Gillot, T.: *The Long-Term Effect of Dietary Supplementations with Fish Lipid Concentrate on Serum Lipids, Bleeding Time, Platelets and Angina. Atherosclerosis* 50: 3-10 (1984).
- (20) Simons, L.A., et al.: *On the effects of dietary n-3 fatty acids (Maxepa) on plasma lipids and lipoproteins in patients with hyperlipidaemia. Atherosclerosis* 54: 75-88 (1985).
- (21) Sotert, N.A.; Lewis, R.A.; Corey, E.J.; Austin, F.K.: *Local effects of leukotrienes (LTC₄, LTD₄, LTE₄ and LTB₄) in human skin. J. Invest. Dermatol.* 80: 115-119 (1983).
- (22) Sperling, R.J.: *Effects of dietary fish oil on leucocyte leucotriene and PAF generation and on neutrophil chemotaxis. In: Simopoulos, A.P., et al.: Health effects of omega-3 polyunsaturated fatty acids in seafoods. World Rev. Nutr. Diet.* 66: 391-400 (1991).
- (23) Stenson, W.F.; Cort, C.; Rodgers, J.; Burakoff, R.; et al.: *Dietary supplementation with fish oil in ulcerative colitis. Ann. Int. Med.* 116: 809-814 (1992).
- (24) Varming, K.; Espersen, G.; Schmidt, E.B.: *Fish oil reduces neutrophil chemiluminescence. Eur. J. Clin. Invest.* 21, 11: 72 (1991).
- (25) Willich et. Al.: *Dtsch. med. Wschr.* 120: 227 (1995).
- (26) Ziboh, V.A.; Casebolt, T.L.; Marcelo, C.L.; Voorhees, J.J.: *Biosynthesis of lipoxigenase products by enzyme preparations from normal and psoriatic skin. J. Invest. Dermatol.* 83: 426-43 (1984).

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