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Translation by Marco Gambetti

FOREWORD

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It is a pleasure for me to introduce this collection of scientific papers published by the "Zone Academy". I have a longstanding relationship with the Academy, also through the Paolo Sorbini Foundation whose aim is to disseminate advances in nutritional research on the specific topic of essential fatty acids.
For many years, this field has been the focus of research in my Department at Milan University and much is also being done by the Zone Academy together with the Barry Sears Inflammation Foundation in Boston, United States.
I would define this collection of papers as a "simple" dissemination of scientific knowledge: it has the merit of offering a clear and accurate overview of a highly topical subject at different levels deserving in-depth analysis. A good dissemination of information can start from this "selection" of articles. Albeit sufficiently "technical", these papers are straightforward and the analytical index makes them easy to consult.
Under my coordination and with the collaboration of Gigliola Montorfano, Manuela Negroni, Paola Corsetto and Angela Maria Rizzo, the Department of Molecular Sciences Applied to Biosystems at the Faculty of Pharmacy, Milan University recently published a scientific paper entitled "Omega-3 fatty acids, biochemistry, sources, functions and use as nutritional biomarkers". Before inviting you to read the report, I intentionally cite a summary of the article published in the journal L'Integratore Nutrizionale - 2009, 12(3) - as the best invitation to enter into the merits of this newly published report.
"Dietary changes in the last century have led to a significant increase in the intake of saturated fatty acids and omega-6 polyunsaturated fatty acids (PUFA) with a concomitant decrease of omega-3 PUFA intake. Greater fish consumption has proved a concrete means of increasing the benefits of long-chain omega-3 PUFA like docosahexaenoic acid by means of dietary intake, and restoring more balanced ratios of omega-6/omega-3. In some cases, when dietary intake is insufficient, ad hoc food supplements may prove a promising remedy".
I hope you will enjoy reading these papers.

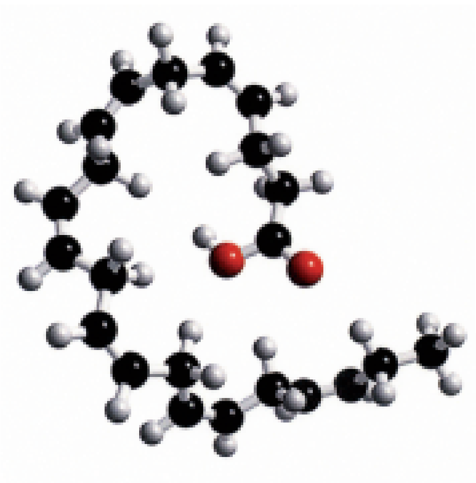
INTRODUCTION

Equipe Enervit

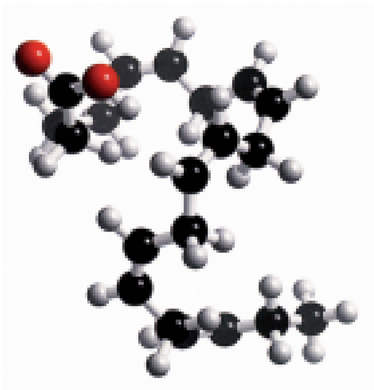
CHARACTERISTIC OF OMEGA-3 FATTY ACIDS

Omega-3 are polyunsaturated fatty acids. This means that they have two concomitant features: on the one hand they are essential to man's well-being and survival, on the other they cannot be synthetized by the human body.

Linolenic acid is an omega-3 fatty acid also found in vegetable foods, but the omega-3 fatty acids useful to man are the long-chain acids EPA and DHA of marine origin. EPA is eicosapentaenoic acid containing 20 carbon atoms and five double bonds, while DHA is docosahexaenoic acid containing 22 carbon atoms and six double bonds. Although the body contains enzymes able to lengthen the carbon chain of linolenic acid, in practice only a minute amount of linolenic acid can be turned into EPA and DHA. For this reason these fatty acids must be consumed in the diet or through supplements.



DHA

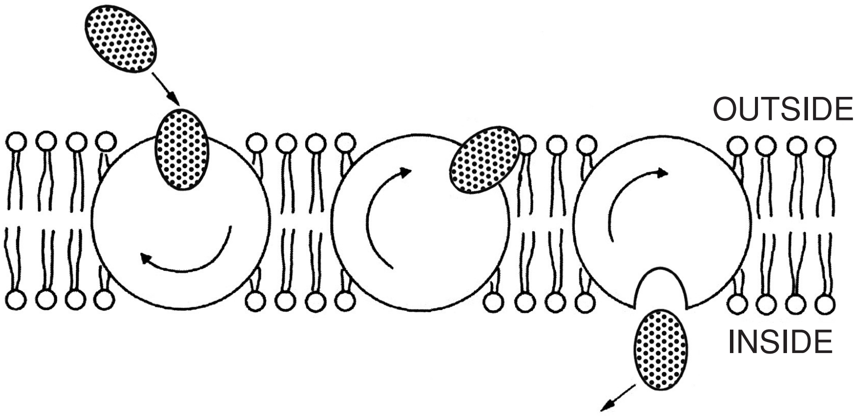


EPA

< Omega-3 fatty acids have a double bond between carbon atoms in positions 3 and 4. Numbering of carbon atoms starts from the last carbon in the chain, known as the "omega carbon" so that the fatty acids with this bond are known as **omega-3**. As the last carbon is also called "n", these fatty acids are also known as **n-3**. Fatty acids are indicated by the letter C followed by the number of carbon atoms present in the carbon chain and a colon followed by another number specifying the double bonds present in the fatty acid. Eicosapentaenoic acid, for example, has 20 carbon atoms and 5 double bonds. As it has a double bond between the third and fourth to last carbon atom it is written as: **C20:5 omega-3**. Instead, docosahexaenoic acid has 22 carbon atoms and 6 double bonds and is written as **C22:6 omega-3**.

THE IMPORTANCE OF OMEGA-3 FOR THE BODY

The presence of many double bonds gives omega-3 polyunsaturated fatty acids a less rigid conformation enhancing their function and increasing the **fluidity of biological membranes** containing polyunsaturated fatty acids. Numerous scientific studies have shown that many of the positive effects correlated to the presence of omega-3 fatty acids within membranes depend on the increased fluidity of such membranes. These effects are thought to allow membrane proteins acting as carriers (transporters) to increase their transport function per unit of time from inside to outside the cell and hence enhance cell activity as a whole. Experimental research, for example, has shown that when the striated muscle fibre membrane is rendered more fluid thanks to the use of omega-3 fatty acids, the insulin molecule is transported more easily thereby



The mechanism of protein transport: the protein is rotated in turn to face the inside and outside of the cell. >

enhancing the insulin response.

Omega-3 fatty acids are a key component of the body's cell membranes, including those of platelets, red and white blood cells. These acids have a positive impact on the cardiovascular system with an anti-atherosclerotic activity regulating the tone of the blood vessel walls. They also serve to control platelet aggregation.

Daily intake of omega-3 fatty acids reduces the risk of cardiovascular disease (stroke, heart attack), lower limb arteriopathies and diabetes, and has other biological effects (anti-inflammatory, positive effect on fats circulating in the blood, glucid metabolism, arterial blood pressure, etc.) as demonstrated by myriad scientific reports.

The effects of omega-3 fatty acids can be summarized as follows:

- **anti-thrombotic effect:** long-chain omega-3 counteract platelet aggregation thereby reducing the likelihood of thrombus formation;
- **anti-arrhythmic effect:** recent research has documented that omega-3 fatty acids protect heart function;
- **anti-inflammatory effect:** omega-3 fatty acids neutralize the negative pro-inflammatory effects of arachidonic acid ("bad" eicosanoids). Many papers have demonstrated their positive action in improving the course of bowel diseases (ulcerative rectocolitis,

Crohn's disease) and some autoimmune rheumatic diseases recognised as having an inflammatory component;

- **effect on the immune system and growth factors:** omega-3 can modulate the immune response and the activity of growth factors due to their effect on cells and cell proliferation (tumours and cancer);
- **effect on the brain:** a fifth of our brain weight is made up of essential fatty acids which play a key role in the transmission of nerve signals. Many studies have described the relations between omega-3 and neurological and psychiatric diseases;
- **effect on foetal development**, namely the central nervous system: as cell membrane components, omega-3 fatty acids are responsible for the proper development of the brain, sight, heart and arteries during the foetal period. Pregnant women need to take omega-3 to ensure sufficient amounts of DHA to transmit to the foetus from its formation. During the last weeks of pregnancy and in the first months of life, development of the retina and brain is completed. These organs are particularly rich in DHA which is essential for optimal function.

Briefly summarizing, it can be said that:

- **EPA** is the fatty acid modulating the balance between "good" and "bad" eicosanoids;
- **DHA** is the basic fatty acid for brain structure.

Omega-3 fatty acids on the market

Many products containing omega-3 fatty acids are currently available on the market, but they are not all the same. Purchasers of these supplements must be certain of their high quality which is guaranteed by internationally recognized bodies.

First and foremost, the best product to use for healthy and correct food supplementation must be based on **top quality raw materials**.

Fish oil must be obtained by a modern method to ensure there are no contaminants. The **analyses** to establish the quality of a supplement are based on **colour detection** and the transparency of fish oil (EPA and DHA fatty acids are transparent molecules), the absence of harmful substances like trans fatty acids, i.e. molecules which have undergone a transformation making them hazardous (they raise the level of LDL bad cholesterol and reduce the level of HDL good cholesterol carrying a cardiovascular risk) and impurities - similar to the plastic - formed during fish oil processing.

A safe, optimal healthy supplement must have the top five star rating by IFOS, an independent Canadian body recognized by the World

Health Organization (WHO). Certification guarantees the quality of the omega-3 in terms of purity, lack of contamination, concentration of active ingredients, shelf life, clinical and physiological benefits. The results of analysis are public and available on the website www.ifosprogram.com, so that the certificate is accessible to consumers at any time.

Why it is useful to take omega-3 fatty acids

Omega-3 intake in industrialized countries has dropped drastically in recent decades due to a diet rich in refined foods and increasingly poor in omega-3 for a number of reasons. To meet the body's need through diet large quantities of fish should be consumed daily. Appropriate supplementation is therefore required.
Fish rich in omega-3 include: herring (around 1 g per 100 grams), carp (around 1.5 g), mullet (around 2 g), salmon (around 1.5 g), mackerel (little more than 2 g), tuna (around 1 g), trout (around 1 g). Fish living in open seas are richer in omega-3 because they have a varied diet that includes algae.

The following is the recommended daily intake for healthy individuals:

- Children (4 to 14 years), women (from 15 years, including pregnancy and breast-feeding) up to **2 grams a day**,
- Adult men from 15 years up to **3 grams a day**

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GLOSSARY

EICOSANOIDS: hormones derived from polyunsaturated fatty acids whose molecule contains 20 carbon atoms. They are produced in all cells in the body and act on the environment surrounding the cell with positive ("good" eicosanoids) and negative ("bad" eicosanoids) effects.

ESSENTIAL FATTY ACIDS: fats the body is unable to synthetize and hence require dietary intake. They are the raw material for the production of eicosanoids. They are divided into groups (omega-3, omega-6, omega-9) giving rise to different eicosanoids.

ARACHIDONIC ACID (AA): an essential fatty acid, the precursor of "bad" eicosanoids. AA is found in the fat of red meat, egg yolk, offal and in certain vegetable oils.

PUFA: Poly Unsaturated Fatty Acids.

HEART

OMEGA-3 FATTY ACIDS: EFFECTS ON CARDIOVASCULAR DISEASE

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Scientific Coordinator of Equipe Enervit

A great number of scientific papers, including the investigation comparing Inuit and Danish populations (Dewailly et al., 2001,) have highlighted a correlation between modified nutritional habits, changes in the omega-3 and omega-6 ratio (a direct consequence of the dietary regime currently adopted in the Western world) and a steady increase in the rate of cardiovascular diseases in the last 150 years.
Most of the articles show that fish intake involves a lower incidence of coronary heart disease and ischemic stroke. Reducing the number of these cardiovascular events (diseases that are the main cause of death in Western countries) reduces mortality from any cause (Hooper, 2006). Several authors have attributed this protective role played by fish to the high content in omega-3 fatty acids found in diets rich in this type of food.

OMEGA-3 FATTY ACIDS AND CARDIOVASCULAR DISEASE

Many studies, both clinical and epidemiological, have shown a lower incidence of cardiovascular diseases in the populations whose diets involve a high consumption of fish, the main source of omega-3 fatty acids. Similarly, reduced risk of sudden death after myocardial infarction has been found in patients receiving omega-3 supplements.
According to some investigators the antiarrhythmic action exhibited by omega-3 may be related to the ability of these fatty acids to affect certain functional parameters of the cardiac cell membrane (changing its lipid composition), and also to their anti-inflammatory properties.
The well known study on United States nurses (Nurses Health Study, NHS), carried out on more than 100,000 nurses followed for several decades by the Harvard School of Public Health in Boston (Hu et. al., 2002), revealed that the nurses who reported a high fish

intake had a significantly lower coronary risk than those who reported only limited fish consumption.

The group with regular fish consumption, at least twice a week, was associated with a 30% drop in the risk of developing a major coronary event if compared with women who had fish less than once per month. This association was confirmed when fish consumption was replaced by intake of omega-3 supplements.

THE GISSI STUDY

The Italian Group for the Study of Survival in Myocardial Infarction (GISSI - Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) originated in 1984 from the partnership between Istituto Mario Negri and the National Association of Hospital Cardiologists (ANMCO Associazione Nazionale dei Medici Cardiologi Ospedalieri). It is currently considered one of the best research groups in the field of cardiovascular diseases. GISSI has produced a great deal of large-scale clinical investigations involving more than 60,000 patients with myocardial infarction.

The GISSI 1 study showed that thrombolysis (pharmacological treatment to reduce vascular occlusions) decreases the infarct-related death rate. GISSI 2 and GISSI 3 generated important information on other treatments to be associated with thrombolysis. In particular, GISSI 3 showed that early administration of ACE-inhibitors after myocardial infarction further improved survival.

The GISSI Prevenzione study focused on patients who had already suffered infarction and compared the effectiveness of omega-3 polyunsaturated fatty acids, vitamin E and statins in reducing mortality and incidence of reinfarction. The most significant result was a 20% drop in mortality among patients who had been given 1 gram of omega-3 fatty acids for three and a half years. Over the whole study period, approximately a 30 % reduction in hospital mortality was recorded. In contrast, the daily intake of 300 mg vitamin E did not produce any beneficial effects. The part of the investigation devoted to studying the effects of pravastatin was stopped early because of the publication of the CARE study results, which clearly showed the benefits of this drug in a similar population.

ANTITHROMBOTIC ACTION

The first effect of omega-3 fatty acids reported in the literature was their antithrombotic action. Several scientific studies have documented the biological activities of eicosanoids and the antagonism between "bad" eicosanoids, which promote aggregation and vasoconstriction and "good" eicosanoids, which have antiaggregant and vasodilating properties. As a result of these effects, the **intake of adequate doses of omega-3 provides an effective and significant antithrombotic action**.

ANTIARRHYTHMIC ACTION

Omega-3 fatty acids can also influence some of the fluidity, and functional parameters of the cell membrane, thus developing an antiarrhythmic action. This happens because all long-chain fatty acids, including omega-3, are incorporated in the lipid portion of the cell membrane. The presence of many double bonds has an impact on membrane fluidity, which in turn affects the action of a large number of membrane proteins including those that have a role of channel or of specific carrier. Some published scientific investigations have in fact shown that the antiarrhythmic action of polyunsaturated omega-3 fatty acids is due to effects on cell membranes. On the contrary, those fatty acids with a rigid molecular structure, like trans fats, play an opposite role (Leaf, 2001; Katz, 2002).

EFFECTS ON BLOOD LIPIDS

The main impact **that omega-3 fatty acids exert on blood lipids is to reduce triglyceride concentration**. The drop in blood triglycerides is correlated with their basal value: in the case of low or normal values, the administration of omega-3 fatty acids does not cause any significant decrease, whereas high basal values are proportionally affected by these compounds (Harris, 1997).
Omega-3 induce a marked decline in triglyceride synthesis by the liver and determine an increase in mitochondrial beta-oxidation. They play a beneficial role in promoting the rise of HDL levels (good cholesterol) while having no significant effect on LDL (bad cholesterol) plasma levels.
The mechanism of action of omega-3 fatty acids on blood lipids is presumably their ability to bind receptors in the cell nucleus that control the synthesis of apolipoproteins and lipolytic enzymes.

EFFECT ON ARTERIAL BLOOD PRESSURE AND VASCULAR TONE

Omega-3 fatty acids are able to control arterial blood pressure and vascular tone by means of several mechanisms. Firstly, they compete, within cell membranes, with omega-6 acids that are responsible for the production of unfavourable substances (negative prostaglandins), which induce constriction of blood vessels with a subsequent increase in blood pressure. Omega-3 fatty acids, on the contrary, promote increased production of favourable prostaglandins, which induce vessel dilation. Alongside this dilating mechanism, omega-3 have several other effects that help explain the resulting reduction in blood pressure values.

The mechanisms promoted by omega-3 fatty acids that are involved in vascular and pressure regulation include:

- increased production/release of nitric oxide;
- lower plasma concentration of noradrenaline;
- regulation of intracellular calcium storage;
- enhanced plasma membrane fluidity.

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MIND AND BRAIN

OMEGA-3 FATTY ACIDS: BENEFITS ON CEREBRAL FUNCTIONS

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Lipids in diet, and more specifically omega-3 polyunsaturated fatty acids, were initially thought to influence the brain only by means of their effects on cardiovascular physiology. Nowadays, however, the scientific community is increasingly focusing on them because of their multiple direct actions on the nervous system

THE EVOLUTION OF THE BRAIN IN THE DEVELOPMENT OF THE HUMAN SPECIES

The importance of omega-3 fatty acids for our brain is demonstrated first and foremost by the history of the development of our own species. Intake of omega-3 is the most studied case of interaction between food and evolution of the brain. DHA is the most commonly found fatty acid in neuron cell membranes. Human biochemistry is not able to produce this nutrient efficiently, which means that the lipid composition of our brains depends mostly on DHA supplied through food. Many scientists believe that when our ancestors in the savannah of eastern Africa introduced omega-3 fatty acids into their diets, the development of their intellectual faculties received a significant boost with marked growth in brain mass, an evolutionary process, which is known today as "encephalization" (1).

Approximately 150,000 years ago humans came across a source of this nutrient, most probably molluscs and crustaceans, which became an integral part of their food habits. Around 40,000 years ago, the intake of these marine-origin fats increased thanks to the introduction of fishing and the associated consumption of several types of fish. As if by coincidence, the great quantum leap in human cultural evolution occurred 40,000 years ago. As 30% of the lipids in the brains of modern human beings are made of DHA, the critical role of this fat is easily appreciated. It is essential to maintain brain functions and neuronal cell membrane integrity, nerve-cell excitability as well as the efficiency of nerve transmission. An adequate intake of DHA through the diet is fundamental to ensure ion permeability of membranes and proper working of transmembrane receptors that support synaptic transmission and, ultimately, cognitive abilities.

THE CENTRAL NERVOUS SYSTEM: FROM EMBRYONIC DEVELOPMENT TO THE FIRST YEARS OF LIFE

The role played by this fatty acid in the proper formation of the central nervous system is crucial from the first phases of embryonic development (2). Deficiency of this substance is connected with brain abnormalities of varying severity. Moreover, evidence has been produced showing that even a slight fatty acid deficiency during pregnancy is associated with negative effects on the newborn's brain functions.

Fish is the main source of DHA. Even if fish consumption is usually recommended, there are studies that advise women to limit seafood intake during pregnancy to avoid possible ingestion of high doses of contaminants, including mercury and dioxin that may accumulate in fish on account of marine pollution. While the principle is correct, the benefits of fats on the brain exceed the toxic effects of pollutants. A large observational study has recently questioned the recommendation to limit fish intake during pregnancy, highlighting the fact that the amount of fatty acids supplied by two weekly portions of fish (340 g being considered the ideal quantity during pregnancy) could be insufficient for the baby's brain development (3).

The authors of the investigation made use of the ALSPAC (Avon Longitudinal Study of Parents and Children) study performed in Bristol, United Kingdom, with a view to identifying the environmental factors such as diet that impact the child's health during and after pregnancy. The study recruited 11,875 women at 32 weeks' gestation. They completed a questionnaire on their nutrition and, in particular, on seafood consumption. Two biochemical markers were employed to validate the frequency of seafood intake: DHA in red blood cells and mercury in the umbilical cord.

The purpose was to compare – by means of specific assessment scales – brain development as well as cognitive and behavioural outcomes in children, age 6 months to 8 years, of women consuming no seafood, from 1 to 340 g per week and more than 340 g per week. The first remarkable result was that 65% of the participants remained below the limit of 340 g of seafood per week; 23% ate more than 340 g per week and 12% ate no fish during pregnancy.

Large observational studies have demonstrated the benefits of a significant supply of fatty acids for foetal brain development and shown that the previously recommended value of 340 g weekly (two portions of fish) for pregnant women is not sufficient.

The study showed that an intake of less than 340 g was associated with a higher risk of children being included in the group with the lowest verbal IQ compared with children whose mothers had reported higher seafood consumption.
The lowest levels of fish intake were associated with suboptimal outcomes for prosocial behaviour, fine motor, communication and social development scores. Eating large amounts of seafood during pregnancy, therefore, did not have any negative impact on the children's cerebral development. On the contrary, beneficial effects were observed. According to the authors, this is sufficient reason to consider the 340 g limit for seafood intake by pregnant women as inadequate. The role of omega-3 fatty acids in stimulating brain functions is not confined to embryonic development. It persists also after birth.
During breastfeeding, women are very efficient in transferring large amounts of omega-3 taken through the diet into the milk produced by the mammary glands, which is further evidence of the paramount importance of these fats during the first months of life.
While this behaviour is fundamental for the baby's brain development, it is, as we shall see later, also one of the reasons why mothers who become omega-3 deficient on account of this transfer mechanism frequently develop mood disorders.
Additionally, a study by the University of Oslo showed that giving mothers omega-3 supplementation from the 18th week of gestation to three months after delivery resulted in an higher IQ in children 4 years after birth, compared with children of mothers who received omega-6 supplementation (4).

COGNITIVE FUNCTIONS AND MEMORY

Several clinical and experimental investigations have confirmed that omega-3 fatty acids, and DHA in particular, stimulate cognitive processes and memory and, more generally, protect brain functions in adults too. Experimental animal models, for instance, showed clearly that omega-3 deficiency in the diet entails cognitive deficits and involves a severe deterioration of memory and learning skills (5, 6). In humans, a diet poor in omega-3 fatty acids was associated with elevated risk of developing many mental disorders, including ADHD, dyslexia, dementia, depression, bipolar disorders and schizophrenia. Some of the mechanisms through which omega-3 fatty acids impact cognitive processes and neuronal plasticity are now beginning to be understood. It was demonstrated, for example, that DHA supplementation is able to raise levels of brain-derived neurotrophic factor (BDNF) in the hippocampus and enhance recovery of cognitive functions in rats following induced brain trauma (7). In the brain, omega-3 fatty acids can activate several metabolic pathways that modulate the expression of cellular factors including the above-mentioned BDNF and insulin-like growth factor 1 (IGF1). These molecules are active at a pre- and post-synaptic level thus triggering various signalling systems such as MAP kinase and calcium/calmodulin-dependent protein kinase which, in turn, facilitate nerve transmission and promote what is known as long term potentiation, a synaptic mechanism that is directly linked with memory and learning processes. DHA's role in elevating BDNF also explains how this fatty acid can interfere with other cell signalling mechanisms, including phosphoinositols and mTOR, which are involved in neuronal plasticity and cognitive processes.

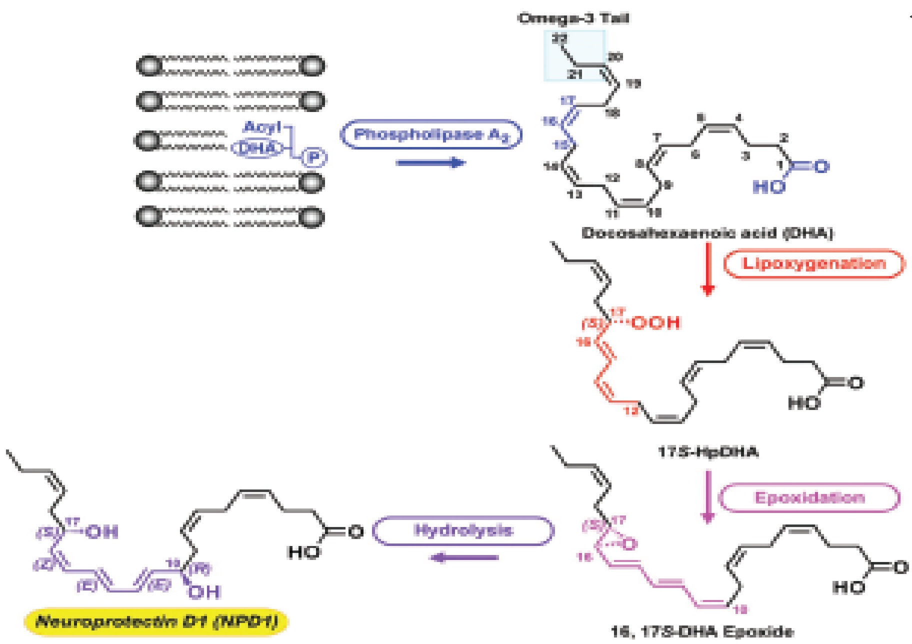
Some studies focused on the effect of omega-3 supplementation on children's school performance (8). A randomized double blind trial divided children into two groups: one received omega-3 while the other was given placebo. The investigation was carried out in a large number of schools in County Durham, United Kingdom (9). The children enrolled in the study presented a certain degree of limited learning potential and concentration ability but an absence of behavioural diseases. They were followed for several months and assessed through different cognitive tests. The trial demonstrated that omega-3 supplementation resulted in improvements in school performance in the children receiving active treatment. These results match those of similar studies carried out on school-age children in Australia and Indonesia that showed omega-3 supplementation (DHA 88 mg/day, EPA 22 mg/day) can boost school performance after 6 or 12 months treatment (10). Adequate omega-3 levels seem to play an essential role in preserving the right mood state, and their administration has been proposed in the treatment of disorders such as depression and anxiety. Some investigations have indeed highlighted that the fall in omega-3 levels in breastfeeding mothers (who lose large amounts of fatty acids in the production of milk for their babies) is tied to the onset and higher intensity of post-partum depression. Additionally, a large epidemiological study showed that areas with high seafood consumption, like Japan and Scandinavian countries, experienced the lowest rate of post-partum depression in the world. At the same time, countries where fish in the diet is limited, like France and Germany, reported the highest incidence of the disease (11).

Among clinical trials, many of the studies on man were aimed at assessing omega-3 impact in reducing cognitive deficits associated with psychiatric disorders. Other investigations highlighted interesting effects on mood states and the treatment of depression and anxiety.

This interesting correlation applies to many other mood and behavioural disorders in children and adults alike. Evidence of the correlation between low omega-3 concentrations and several psychiatric disorders led to the use of these fatty acids in the

treatment of some **behavioural and mood disorders**.
One study involving bipolar patients and another sufferers of primary psychosis showed that EPA improved psychiatric symptoms substantially. A recent metanalysis showed that omega-3 supplementation is able to reduce symptoms in depression, but not in the treatment of manic disorders (12).

The extent to which omega-3 fatty acids can be considered as a treatment, or perhaps an adjuvant, in the field of psychiatric disorders has, however, not yet been established. Moreover, their role in brain physiology does not seem limited to behavioural aspects only. Indeed, numerous studies indicate an important protective function exerted by omega-3 fatty acids also in many neurodegenerative diseases, from Alzheimer's to amyotrophic lateral sclerosis. Recent investigations suggest that DHA may play an important role in protecting neurons from oxidative stress and inhibiting synthesis of pro-inflammatory and pro-apoptotic genes in the brain and retina. It was discovered that DHA's metabolites, active molecules named docosanoids, include Neuroprotectin D1 - a substance with powerful antioxidative and antiapoptotic properties also able to inhibit cyclooxigenase 2 (13). Starting from this evidence, some studies were able to demonstrate the ability of DHA and neuroprotectin D1 to protect our brains from pathological ageing and neurodegenerative diseases.



< Biosynthesis of neuroprotectin D1 (NPD1). A DHA-containing phospholipid membrane is hydrolized by phospholipase A2 with production of free DHA. The carbon atoms in DHA are numbered and the omega-3 tail is highlighted. Lipoxygenation is followed by epoxidation and hydrolysis and **finally NPD1 synthesis**.

(from: N.G. Bazan: Homeostatic regulation of photoreceptor cell integrity: significance of the potent mediator neuroprotectin D1 biosynthesized from docosahexaenoic acid: the Proctor Lecture. Invest Ophthalmol Vis Sci. 2007 Nov; 48(11): 4866-81)

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REACTIVITY AND MOOD

OMEGA-3 FATTY ACIDS: POSITIVE EFFECTS ON COGNITIVE FUNCTION

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REACTION TIMES - POMS

A large number of scientific studies have demonstrated that omega-3 fatty acids have a substantial impact on the activity of the nervous system. In particular, these fatty acids improve nerve transmission and permeability of neuronal membranes. Hence, our starting hypothesis was that they could also exert some influence on complex brain functions, including cognitive processes, reaction times and mood. A study was carried out on two groups of healthy subjects for a period of 35 days. One group was given omega-3 supplementation while the control group received placebo (olive oil).

The results obtained demonstrated favourable effects on reactive and cognitive skills, mood and emotional control, information processing and reactivity. Reaction times were assessed by means of tests measuring the interval elapsing between ideation and execution of a rapid movement (alert) or other types of activity (go/no-go, choice, sustained attention). For each test, reaction times (in milliseconds - ms) and variability index (VI) were recorded. The "alert" test, for instance, measures simple reaction times when subjects sitting before a screen must respond as fast as possible to the appearance of a red circle on the screen by pressing a key. In the group of tests measuring complex reaction, significant improvements were recorded in the go-no go-test (measuring the decision-making skills of the subject who has to press different keys following the appearance of specific inputs in the form of different figures) and sustained attention (a series of figures are presented sequentially and the subject must recognize if a figure is the same as the previous one in colour, shape and size). Data showed a significant improvement of complex reaction times.

Mood was studied by means of the Profile of Mood States (POMS) test, which proved very useful to assess psychological profiles. In the test, subjects are requested to answer questions on their feelings and give a certain score. The answers are processed and values obtained for positive feelings (vigour) and negative ones (anger, tension, confusion, depression, fatigue). This test showed that after administration of omega-3 vigour goes up while negative feelings decrease. The effect of omega-3 is confirmed by other sets of data:

(a) heart rate variability, showing a reduction in cardiac sympathetic tone usually associated with high levels of stress;
(b) EEG frequencies, showing a reduction in high frequencies which are also associated with high levels of stress and anxiety;
(c) lower skin conductance;
(d) blood cortisol levels that drop after omega-3 intake.
Blood tests highlighted a marked reduction in the arachidonic acid/eicosapentaenoic acid (AA/EPA) ratio after omega-3 supplementation.

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PEDIATRICS

OMEGA-3 FATTY ACIDS: POSITIVE EFFECTS ON COGNITIVE FUNCTIONS

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HYPERACTIVITY IN CHILDREN - ADHD

ADHA - Attention Deficit and Hyperactivity Disorder - affects a large number of children; the estimated rate is 3%. These children are not just very active, they suffer from a disease with different levels of severity, based on neurobiological traits, that adversely impacts interpersonal relationships with parents and other children from the first years of life. In most cases, ADHD children are of normal intelligence. The only effective treatment discovered so far is life-long administration of psychotropic drugs with the related side effects. Some researchers have identified a deficiency of omega-3 fatty acids in most of these subjects. Based on this observation, a study was started using EnerZona Omega 3 RX fish oil. This oil is in liquid form and has a pleasant taste. It is a highly purified (pharmaceutical grade) ethyl ester containing EPA and DHA. In these children a deficiency of both these fatty acids has been recorded. Results were really encouraging. The children involved were able to take high doses of omega-3 with very few side effects since the fatty acids were "absorbed" by the tissues that had a real craving for them. The AA/EPA ratio dropped from extremely high to normal levels and almost all children had a long-lasting clinical improvement in terms of less hyperactivity and higher attention levels (approximately 25% overall improvement). Although these findings do not constitute the solution to ADHD, they surely indicate an additional tool in the management of the disorder. As omega-3 is a nutritional supplement, the treatment proposed is more natural and less dangerous than the pharmacological one.

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OMEGA-3 FATTY ACIDS: PREGNANCY AND BREASTFEEDING

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Long-chain omega-3 fatty acids, and in particular docosaexaenoic acid (DHA), are thought to be an essential dietary supplement during pregnancy and breastfeeding to ensure successful pregnancy and excellent child development.

Intrauterine and postnatal growth requires a significant intake of essential nutrients, including polyunsaturated fatty acids. Those with a long chain, in particular the omega-3 fatty acid known as docosahexaenoic acid, are swiftly deposited in brain and retinal tissues during the first phases of development. Taking omega-3 fatty acids has an impact on the outcome of pregnancy. Numerous scientific studies have highlighted how a combination of DHA and EPA during pregnancy can reduce premature deliveries (before the 34th week of gestation) by 31% and the number of high-risk pregnancies by 61%. This is due to a slightly longer duration of pregnancy and a heavier weight of the baby at birth. Additionally, no negative consequence has been recorded when the daily dose of DHA was much higher than 1 g. This preventive effect on premature births suggests that additional benefits in terms of child mortality and morbidity may be expected. Omega-3 fatty acids have a favourable effect on the development of children who receive DHA through the placenta. Transportation of fatty acids takes place by means of a protein carrier, as shown by a study by Prof. Koletzko. In this way the foetus receives the necessary amounts of DHA for tissue growth. The role of the mother is reflected in the DHA content in the umbilical cord at birth and in the DHA concentration in maternal milk. Since foetus and newborn share a marked need for polyunsaturated fatty acids (PUFA), intake of DHA through placenta and maternal milk is fundamental for the brain, other tissues and various functions like visual development, fine motor skills, behaviour, language discrimination and verbal IQ before school age. Data from research on Inuits, a population eating large amounts of fish, show a dose-response relation between DHA levels at birth and during development, even when high doses of DHA are taken. The amount of DHA provided by mothers can also modulate the immune response at birth.

Adequate intake of fatty acids is recommended by the European Commission, renowned paediatrics journals and clinical nutrition societies. The suggested dose is at least 200 mg of DHA. This is the amount that can be provided by two weekly portions of fish. When fish is not eaten in sufficient quantities, supplements should be taken.

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OBESITY

OMEGA-3 FATTY ACIDS: EFFECTS ON LIPID METABOLISM

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One of the properties of omega-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA) is their ability to interact with lipid metabolism in multiple ways. The best documented interaction is modulation of the expression of genes coding for enzymes active in the synthesis or oxidation of fatty acids and in mitochondrial biogenesis. On the basis of this evidence, experimental studies have focused on n-3 LCPUFA with a view to gaining information on their ability to prevent or reduce excess fat tissue.
The purpose of this paper is firstly to summarize biochemical evidence supporting a possible role played by omega-3 fatty acids in controlling adipose tissue originating chiefly from animal model studies, and secondly to review investigations into the efficacy, in particular in humans, of fatty acids dietary supplementation.

PREVENTION AND TREATMENT OF OBESITY

The ability of omega-3 long-chain polyunsaturated fatty acids (n-3 LCPUFA) found in fish, namely docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), to modify lipid metabolism is very well known, so much so that public healthcare institutions consider them a primary therapeutic tool in cases of hypertriglyceridemia, the pathological elevation of fat concentration in blood.
As well as controlling high triglycerides levels, omega-3 fatty acids may be effective in the prevention and control of excess body weight. This paper provides a brief review of the scientific literature regarding the biochemical mechanisms through which omega-3 may promote control of adipose mass in the body. It also examines the studies on man aimed at confirming this hypothesis.
The effects of omega-3 on blood triglycerides and their potential ability to control the fat mass are mediated by nutrigenomic properties (1), i.e. the ability of omega-3 to penetrate the cell nucleus and modulate gene expression. In other words, specific ligands

(in nutrigenomics, molecules taken through the diet like omega-3) penetrate the cell nuclei of various tissues and activate or inhibit nuclear receptors that, in turn, increase or decrease the expression of specific genes. In this case, these are genes coding for enzymes involved in lipid metabolism (2). Essential, if not unique, elements in the mediation of omega-3 effects on lipid metabolism are the receptors known as "peroxisome proliferator-activated nuclear receptors" (PPAR) that carry out important regulatory functions in the metabolism of lipids and other molecules and in fundamental processes like cell differentiation and growth. For an in-depth illustration of PPAR, please refer to the relevant literature (4, 5).

MODULATION OF LIPID METABOLISM

Thanks to their nutrigenomic properties, omega-3 have been demonstrated to modulate lipid metabolism in the liver, adipose organ, bowel and muscle tissue, including myocardial tissue. Convincing evidence has been obtained on the role of omega-3 fatty acids in inhibiting the expression of genes coding for enzyme proteins with lipogenic activity (contributing to fat synthesis), and also in activating the expression of molecules mediating fatty acid oxidation (contributing to fat consumption). (For brevity's sake, the different degree of omega-3 activity found in different tissues cannot be discussed in this paper.)

The lipogenic enzymes inhibited by omega-3 are fatty acid synthase (FAS), acetyl-coenzyme A carboxylase alpha (ACACA) and stearoyl CoA desaturase (SCD-1) (6-10). Additionally, n-3 LCPUFA boost the activity of another enzyme, AMP-dependent protein kinase (AMPK), which inhibits acetyl-CoA carboxylase (catalyzing its phosphorylation) leading to lower production of malonyl-CoA, an intermediate metabolite essential in fatty acid synthesis (11).

The activation of fatty acid oxidation involves both peroxisomal and mitochondrial pathways. Omega-3 trigger both the expression of enzymes catalyzing peroxisomal fatty acid oxidation, i.e. acyl-CoA oxidase 1 (ACOX1), D bifunctional protein (DBP) and 3-ketoacyl-CoA thiolase (12, 13), and the expression of mitochondrial enzymes involved in fatty acid beta oxidation, in particular carnitine palmitoyl transferase 1 (CPT-1), an enzyme facilitating the transfer of acyl groups inside mitochondria where they can be oxidized (12, 14). Since fatty acid peroxisomal oxidation causes a 30% higher thermal dispersion of energy, which translates into 30% less APT synthesis compared with mitochondrial oxidation, its activation involves a higher fatty acid oxidation requirement for the same level of ATP production (15). In addition to these mechanisms inhibiting the synthesis of fatty acids or activating their

oxidation, omega-3 would appear to produce an increase in the levels of uncoupling protein 2 (UCP2) in the heart and liver (13, 16), and UCP3 in the skeletal muscle (13). This means partial uncoupling of mitochondrial oxidation processes from ATP phosphorylation and, consequently, more energy dispersion, in the form of heat in mitochondria too.
Apart from boosting the synthesis of enzymes involved in oxidation, omega-3 also promote this catabolism through stimulation of mitochondrial biogenesis, i.e. by promoting an increase in the number of mitochondria. This effect is mediated by the role of AMPK in activating nuclear respiratory factor 1 (NRF-1) (10, 18) and PPARγ coactivator 1α (PGC-1α) (10), both of which are nuclear factors regulating the transcription processes of the genes involved in mitochondrial biogenesis.

With the purpose of testing the molecular effects described so far, adipose tissue (white adipose tissue) and liver were selected since they seem to be the main target organs in a dietary strategy based on omega-3 fatty acids aimed at controlling adipose mass. **Recent research, however, seems to suggest that bowel lipid metabolism may also play an important role in the pathogenesis of obesity** (19). Even if the small bowel's main function in lipid metabolism is triglyceride resynthesis and their secretion into the lymphatic system in the form of kilomicrons, it also produces enzymes involved in fatty acid beta oxidation in amounts comparable to that found in the liver (20, 21). When the diet includes omega-3 supplementation, these amounts rise significantly (22, 23).

Another potentially interesting field in the study of omega-3 properties in terms of adipose mass control is their antiproliferative effects and the role in adipocyte differentiation. The mass of white adipose tissue can grow though hypertrophy (greater volume of the existing cells) or hyperplasia (increase in the number of cells). Hyperplasia results from activation of a cell differentiation process that originates from stem cell precursors and develops through intermediate stages of mesenchymal cells, multipotent cells, preadipocytes and, lastly, mature adipocytes (24, 25). Omega-3 supplementation, specifically DHA, has been originally associated with inhibition of cell proliferation (26), adipocyte differentiation into the mature form (27) and increased apoptosis, i.e. programmed and organized death of mature adipocytes (27, 28). It is not known yet how omega-3 fatty acids exert this effect against proliferation and differentiation in adipocytes. One hypothesis involves changes

While dietary omega-3 fatty acid supplementation (6 g of fish oil daily) does not change basal metabolism, it determines - through the modulation of genes in the liver and many other tissues - a reduction in the respiratory quotient and an increase in lipid oxidation at rest.

in the composition of cell membranes and eicosanoid synthesis that occur after dietary omega-3 supplementation (3).

ANTI-INFLAMMATORY ACTIVITY ON ADIPOSE TISSUE

The final area in the analysis of omega-3 impact in the control of adipose mass is the role that these fatty acids may play in modulating the secretion of adipokines, that is cytokines produced by white adipose tissue. In obesity, white adipose tissue frequently shows signs of an ongoing inflammatory process (29) with the involvement of macrophage infiltration and release of proinflammatory adipokines which are, most probably, the connection between obesity and its related diseases, such as insulin resistance, diabetes mellitus, arterial hypertension, high blood triglycerides and, ultimately, cardiovascular risk (30).

In an experimental study on mice, dietary omega-3 supplementation proved to be effective in preventing inflammatory infiltration of white adipose tissue in a high fat-content diet (31).

Though production and release of almost all inflammatory adipokines rise with the growth of white adipose tissue mass, this does not apply to adiponectin, a special adipokine with anti-inflammatory and insulin-sensitizing activity. When inflammatory adipokines grow, release of adiponectin by white adipose tissue decreases and tends to be inversely proportional to the mass of adipose tissue (32). With reference to adiponectin's anti-inflammatory and insulin-sensitizing properties, dietary omega-3 supplementation, DHA in particular, has proved effective in promoting the release of this adipokine that could be a fundamental element in the mediation of their insulin-sensitizing effect (3).

Experimental evidence on the effect of omega-3 on other adipokines, such as leptin, is for the moment very weak and controversial (3).

Experimental investigations focusing on the actual ability of omega-3 fatty acids to prevent or reduce excess storage of white adipose tissue were conducted both on animal and human models. Animal studies, which are fundamental for a full appreciation of cellular and molecular mechanisms, will not be illustrated here for reasons of space and because the high doses frequently required by experimental protocols would not be applicable to humans.

The effects of omega-3 fatty acids on inflammatory infiltration of white adipose tissue and on the production of pro- and anti-inflammatory cytokines may help obese subjects restore proper metabolic conditions for fat mass control.

RESEARCH ON FAT MASS CONTROL

In humans, different experimental protocols have been tested: a) omega-3 dietary supplementation as the only potentially useful factor in controlling fat mass; b) omega-3 supplementation in the framework of a low-calorie diet; c) omega-3 together with a physical exercise programme; and d) omega-3 fatty acids associated with both physical exercise and low-calorie diet.

In some of the studies, use of omega-3 as the only means to control fat mass without any form of physical exercise or low-calorie diet, has led to decreased respiratory quotient and increased lipid oxidation at rest (17). Other authors showed that omega-3 fatty acids can determine a change in weight and body composition, assessed with hydrostatic weighing, only if associated with physical exercise (33), while omega-3 supplementation produced a significant change in body composition of subjects as shown by DEXA, with reduction of fat mass and adipocyte diameter in subcutaneous periumbilical fat (34).

When research protocols included omega-3 supplementation and a low-calorie diet (35, 36, 37, 38, 39) or supplementation associated with physical exercise without caloric restriction (40, 41), the observed decline in body weight and fat mass (DEXA) was probably related more to reduced caloric intake or increased physical exercise than to any specific action by fatty acids.

Another study focused on the effects of omega-3 supplementation associated with both low caloric intake and physical exercise (42). Data showed greater weight loss and reduction in hip circumference in the group receiving omega-3 fatty acids (2.8 g/day; EPA:DHA ratio 2:1).

To conclude, experimental research on animals highlighted several effects produced by omega-3 fatty acids, in particular regarding modulation of the expression of genes involved in lipid metabolism in various tissues, in terms of both fatty acid synthesis and oxidation. In addition to these biochemical effects, some information has been obtained on the possible role of omega-3 dietary supplementation on proliferation and differentiation of adipocytes and adipokines. Evidence of this is, however, still limited. Furthermore, most of the effects, including the biochemical changes, have been achieved at much higher doses than would ever be taken by humans with food or supplementation. This, however, does not rule out the possibility that even **very few grams per day in humans may significantly prevent the growth of fat mass or contribute to reduce it**, if fatty acids are associated with low-calorie diets or physical exercise, as some studies are indicating.
It is worth remembering that patients with excess body weight usually suffer from insulin resistance or are at risk of developing this,

and frequently manifest the changes induced by metabolic syndrome along with hepatic steatosis. Clinicians are recommended to ensure overweight and obese patients have an adequate intake of omega-3 since these have been shown to be beneficial in fighting insulin resistance (43, 46) thus reducing the risk of clinically relevant comorbidities.

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SPORTS

OMEGA-3 FATTY ACIDS: BENEFITS FOR PHYSICAL EXERCISE AND TRAINING

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A balanced nutritional strategy based on the athlete's caloric requirement with an adequate supply of energy and supplements (vitamins, minerals and omega-3) is fundamental in sports. Athletic performance can be affected by many neuro-psychological factors, including the ability to maintain concentration, control in the execution of motor tasks, reactivity, and speed.
However, the most important role in optimizing performance is played by hormones. They act as vectors that carry information and control virtually every element impacting athletic performance.
Many of the hormones produced by our body can be modulated through diet, in particular through the Zone nutritional strategy and the intake of long chain omega-3 fatty acids, such as EPA and DHA

OMEGA-3 FATTY ACIDS AND INFLAMMATION

Athletes aiming at high-level performance follow very tough training regimes. This implies of course a higher risk of accidents, especially those caused by repeated microtrauma. The consequence is forced rest periods with inevitable loss of efficiency.
The main factors that, according to some authors (Ekstrand and Gillquist, 1982; Lysens et al., 1984), links a higher risk of accidents to more intensive training is excess stress, especially since these cases show a significant increase in blood cortisol, a well known stress hormone. An excessive amount of cortisol involves deterioration of performance with concomitant stimulation of proinflammatory hormones. According to Ostrowski et al. (1998) intense physical exercise induces muscles to produce large amounts of proinflammatory cytokines. Pedersen et al. (2000) showed that levels of interleukin-6 (a typical proinflammatory eicosanoid) increased 100-times following a demanding training session. Since interleukin-6 levels are related to muscle damage, it has a very negative impact on athletes when production of proinflammatory eicosanoids is repeated two or three

times a day and recovery times between "insults" are very short. Additionally, intensive training sessions reduce the production of a series 1 prostaglandins with anti-inflammatory activity. The length of recovery times after training sessions (or competitions) depends on the extent of pro- and anti-inflammatory response. Therefore when the production of proinflammatory hormones is high and the production of anti-inflammatory hormones is low, recovery time is obviously longer and work by the athlete must be limited to lower the risk of accidents.

Athletes who are determined to control the body's inflammatory state can do so by following an anti-inflammatory nutritional approach (like the Zone nutritional strategy) since this reduces production of arachidonic acid, the most influential element in the generation of proinflammatory eicosanoids that cause inflammation (Sears, 2005).

The body's inflammatory response can be further decreased by means of adequate supplementation with fish oil rich in EPA and DHA (Sears, 2005). These long-chain omega-3 fatty acids are able, among other things, to replace part of the arachidonic acid molecules in cell membranes, which leads to lower production of proinflammatory eicosanoids (such as interleukin-6) and higher levels of the anti-inflammatory series 1 prostaglandins (Bagga, 2003; Burns et al., 2007; Grimble, 1998).

In practical terms, this means that omega-3 supplementation can be viewed as a tool leading to fewer accidents, especially in athletes involved in repeated and intensive training sessions.

Smith (2000) put forward the idea that excess cytokine production can be the cause of overtraining, another negative consequence of intensive training much feared by athletes.

OMEGA-3 FATTY ACIDS AND CENTRAL NERVOUS SYSTEM EFFICIENCY

Regular use of long chain omega-3 fatty acids proved to be effective also in improving central nervous system efficiency by boosting certain properties (reaction times and mood state) that can help to enhance performance in several sports.

Combining an anti-inflammatory nutritional approach and omega-3 supplementation reduces the risk of accidents in athletes involved in repeated, intensive training.

Professor Fontani and his colleagues in the Physiology Department of the University of Siena carried out investigations to test the favourable impact of omega-3 on complex nervous system functions, like cognitive skills (2005b). The hypothesis was tested in experiments linking omega-3 administration and Zone Diet, which seems to improve nerve functions. The results obtained in Siena

show beneficial effects on reactive and cognitive skills, mood (measured with POMS - Profile of Mood States), ability to control emotions and responses, and reflexes in general.
Tests generated different profiles for athletes based on different performance levels and showed that after intake of omega-3 fatty acids, vigour increases and negative feelings decrease (see article at pp. 23-24).

OTHER POTENTIAL BENEFITS OF OMEGA-3 FATTY ACIDS IN ATHLETES

Supplementation with long chain omega-3 fatty acids may have other beneficial effects on athletes, although this has still to be confirmed in the field, at least among elite athletes.

According to Sears (2005), for instance, associating the Zone nutritional strategy and fish oil supplementation optimizes eicosanoid production. This in turn produces an increase in capillary diameter, accelerates oxygen transfer to muscles and, consequently, raises aerobic production of ATP, the fuel that muscles require. In elite athletes practicing aerobic disciplines, however, no confirmation has been obtained regarding improvement in oxygen utilization indices after omega-3 intake. The reason for this may be that these athletes have already achieved maximum aerobic efficiency.
Another possible effect caused by omega-3 supplementation is the increase in muscle mass, an essential component of disciplines requiring strength and muscle power: not only throwing disciplines in athletics, weight lifting and body building, but also sprint disciplines, jumps and so on.
During resistance training sessions (aimed at increasing muscle strength and mass) microscopic injuries are produced that trigger synthesis of new proteins, the pillars on which muscle properties can be built. Natural release of a large amount of anabolic hormonal factors (in particular GH - growth hormone) is promoted by following the Zone nutritional strategy associated with regular intake of omega-3 fatty acids.
This is how muscle protein synthesis can be stimulated. Most of the favourable effect on protein synthesis, however, seems to be due more to the Zone nutritional strategy than omega-3 fatty acids.

Combining Zone and omega-3 is also very useful for weight loss purposes. In some sports discipline, athletes are grouped on the basis of their body weight (weight lifting, boxing and other combat sports; lightweight rowing etc.). In these cases, reducing fat body mass without compromising muscles is of paramount importance. With very few exceptions, like sumo or the heaviest categories of weight lifting and combat sports, excess body fat jeopardizes sports performance. Combining the Zone nutritional strategy and omega-3 allows athletes to eliminate excess body fat more efficiently than with the usually recommended diets.

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Control of inflammation and shift from the catabolic to the anabolic phase occur earlier if the inflammatory state of the body is limited.

Notes

Notes