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# Physiological Effect of Exogenous Fatty Acids on Lipid Metabolism and Prostaglandin Precursors*

A. Seher**

*Federal Centre for Lipid Research, Münster, Federal Republic of Germany*

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Lipids are vitally important constituents of all living cells. But the animal organism can not synthesize all the fatty acids, needed for a healthy life. The organism depends on the intake of essential fatty acids, which it gets from dietary fats and oils. The complex effect of digested fats can be understood as combination of 5 different physiological effects of saturated and unsaturated fatty acids:

1. Fats serve as energy supply.
2. They influence the *de novo* synthesis of fatty acids in the metabolism.
3. Fatty acids, which can not be synthesized in the organism, underlie a special storage mechanism.
4. Mixtures of different unsaturated fatty acids show competitive interactions in the metabolism.
5. The sum of these effects has consequences on the formation of prostaglandin precursors.

This disposition will also be the order of the following review

*Energy Supply*

The high energy supply of fats can be mentioned briefly. Its energy contents is-as it is well known-twice that of proteins or carbohydrates. The ß-oxidation of fatty acids as source of energy production is distinctly important for the activity of the heart muscle. Its energy need is supplied by fat oxidation for more than 60%.

*Influence on the de novo Synthesis*

More recent results on the influence of dietary fatty acids on the *de novo* synthesis were received from feeding experiments with growing pigs[1]. Animals were fed isocaloric diets, only differing in the quantity of the same fat. The result was, that the different feeding groups of animals had formed different compositions of depot and organ fats, distinctive of the quantity of fat in the diet. An example is given in Fig. 1.

Fig. 1 shows the behaviour of stearic acid. The dotted line gives the quantity of this acid eaten by the animals. The drawn out line above represents the concentration of stearic acid in the lipids of the heart muscle of the animals.

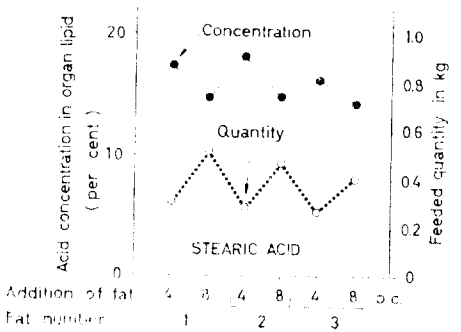


**Fig. 1**: Stearic acid in the heart muscle lipids of pigs.

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** Author's address: Prof. Dr. A. Seher, Bundesanstalt für Fettforschung, Piusallee 68~76, D-4400 Münster, Germany

The two lines take a course against one another. It is well known, that the fatty acid synthesis in the organism yields mainly palmitic and stearic acids, besides oleic acid. The organ and depot lipids of the animals fattened with the low fat diet contained more stearic acid than the lipids from the high fat groups. It is obvious, that the higher supply with exogenous stearic acid decreases the *de novo* synthesis in the animal. Similar observations were made for palmitic and oleic acids.

*Behaviour of Fatty Acids, not Produced by Animal Metabolism*

Fatty acids, which the animals cannot synthesize, themselves, show another—totally opposite—behaviour. This is demonstrated from the same feeding experiment for linoleic acid in Fig. 2.

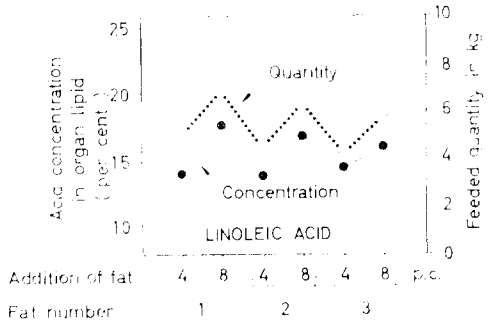


**Fig. 2**: Linoleic acid in the heart muscle lipids of pigs.

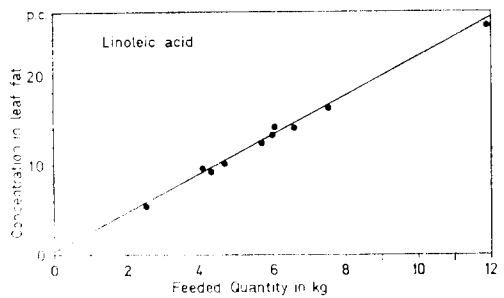


**Fig. 3**: Correlation between concentration of linoleic acid in the leaf fat and the quantity feeded.

It is obvious, that the higher concentration in the lipids corresponds with the higher dose in the feed. Corresponding observations were also made for linolenic acid.

Furthermore, for all fatty acids, which are not synthesized in the animal metabolism a linear relationship between the quantity fed and the concentration in the organ or depot fat was observed (Fig. 3).

Analogous dependences were observed, for linolenic acid or erucic acid too.

*Interactions of Unsaturated Fatty Acids*

In feeding experiments with small laboratory animals it is possible to supply them with isolated purified fatty acids or pure glycerides to investigate the biological effect. Usual nutrition contains natural fats, consisting of mixed fatty acids and triglycerides. Followingly, normal nutrition causes an intake of mixtures of saturated and unsaturated fatty acids.

When feeding young pigs with natural fats, in the livers of the animals a strong depression of the arachidonic acid concentration was observed, despite a slightly increasing supply with linoleic acid. As reason for the decrease a simultanous small increase of linolenic acid intake from 1.7 to 1.8kg during the whole feeding time of 100 days was detected. The cause of this fact might be a competitive hindrance of metabolic transformation of linoleic acid into arachidonic acid by linolenic acid. In this metabolic pathway the firststep is the desaturation of linoleic acid by $\Delta^6$-desaturase.

It has been found a competition between the different unsaturated fatty acids at this enzyme. Besides the quantity of fatty acid, there is a distinct affinity of the enzyme to unsaturation of fatty acid substrates. The $\Delta^6$-desaturase has the highest unsaturated fatty acid. In our example it is the linolenic acid. A decreasing pre-

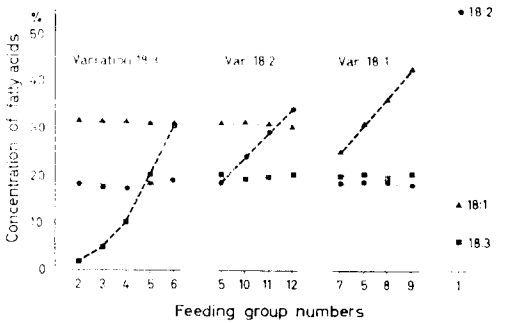


**Fig. 4**: Feeded quantities of unsaturated fatty acids during a period of 100 days.

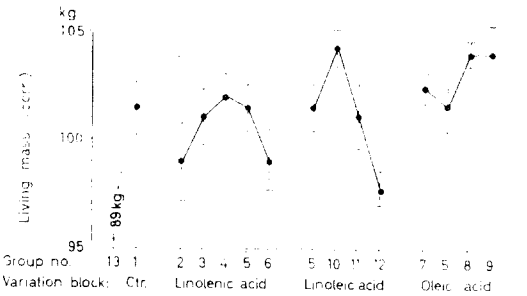


**Fig. 5**: Living masses at the end of the feeding experiment.

ference was found for linoleic acid and at last for oleic acid.

For further studies of the reciprocal action of different unsaturated fatty acids in the metabolism of pigs, young animals were fed mixtures of fats, which had been composed in such a way, that the variations resulted which are shown in Fig. 4.

Besides a control group, number 1, three variation blocks were formed: in each block two of the three fatty acids tested were given in equal amounts, and the third was given in increasing quantities. In the variation block of linolenic acid the animals eat in a growing period of 100 days about 6kg oleic acid, 4kg linoleic acid and increasing quantities of linolenic acid. In the linoleic acid block, 6kg of oleic acid were given together with 4kg linolenic acid. Linoleic acid was fed from 4 to 7kg. In the block of variation of oleic acid the animals got about 4kg of linoleic and linolenic acids respectively. The dose of oleic acid was increased from 5 to 9kg. The fat mixtures were composed by mixing edible fats in such a manner, that in each feeding group the same fat content of 10% per mass was in the fodder. By this means, all animals received an isocaloric diet, containing sufficient amouts of protein, vitamins and mineral salts. Though this strongly equal nutrition, the living mass at the end of the experiment differed surprisingly (Fig. 5).

In the variation of linolenic acid, a weight maximum was observed at the animals, having fattened with a diet containing 10% linolenic

**Table I: Influence of dietary fatty acids on the weights of inner organs (gramms per 100kg of corrected living mass).**

| Organ | Experimental blocks | | Linolenic acid |
|---|---|---|---|
| | Oleic acid | Linoleic acid | |
| Milt | 115～ 116 | 117～ 120 | 117～ 138+18% |
| Heart | 327～ 334 | 353～ 368 | 323～ 364+13% |
| Liver | 1,360～1,398 | 1,404～1,441 | 1,360～1,754+29% |
| Kidnies | 315～ 312 | 329～ 329 | 295～ 398+35% |
| Adrenal glands | 4.4～ 4.4 | 4.7～ 4.3 | 4.8～ 4.7 |
| Thyroid gland | 7.9～ 8.1 | 8.3～ 9.1+10% | 7.5～ 9.4+25% |

acid in the fat. That means 2 energy-% in the diet. Increasing amounts of linoleic acid caused a mass reduction of high significance. Also significant is the rise of the living mass under increasing doses of oleic acid.

Not only the body weight but also the weights of metabolic active inner organs was found to be influenced by the fat composition of the diet (Table I).

The first figures in Table I give the mass of the organ in the animal group having eaten the lowest quantity of the specified fatty acid, whereas the second figures give the masses of the organs from the animal groups having eaten the highest quantity. Oleic acid makes no difference. Corresponding are the observations in the variation of linoleic acid. But 30% per mass linolenic acid in the food fat cause a large increase of the organ weights. Mostly affected are the livers and the kidnies.

In both organs the total lipid content is not affected by the different composition the dietary fat. But a characteristic influence was observed in the composition of the lipids (Fig. 6).

Influenced by increasing amounts of linolenic acid the content of phospholipids is reduced, whilst the portion of triglycerides is increased. A similar effect shows oleic acid. Linoleic acid causes an opposite effect.

A characteristic influence of the dietary fat

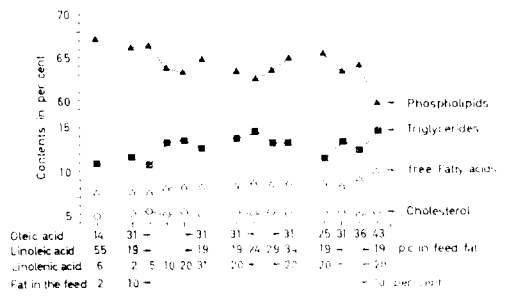


**Fig. 6**: Contents of lipid classes in total liver lipids.

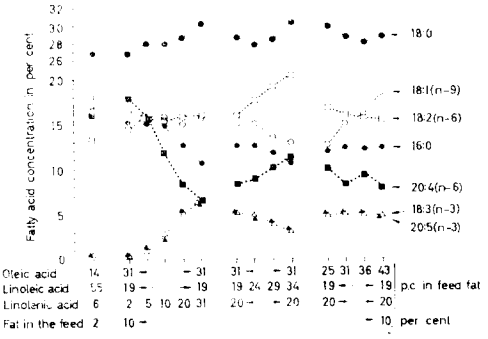


**Fig. 7**: Composition of the fatty acid mixtures in the total liver lipids.

on the fatty acid composition of the liver lipids can be observed (Fig. 7).

Most impressive is the reduction of arachidonic acid by increasing amounts of linolenic acid. Enhancement of linoleic acid in the diet caused an increase of this acid in the liver lipids. This effect is accompanied by a small increase of arachidonic acid in the livers. But, it was impossible to reach the concentration, determined in the animals having eaten the diet low in linolenic acid. Oleic acid has only little effect.

Of special interest is the influence of exogenous fatty acids on phospholipids, as they are important constituents of membranes. Organs very rich in membranes are the kidnies. Followingly, we isolated the phospholipids from the kidnies, separated them into individual classes, and analysed their fatty acid composition.

The first and general observation was, that each class of phospholipid shows ther own and specific answer to the dietary fat. Examples are given in Fig. 8~10.

The three columnes in fig. 8 represent the content of stearic acid, arachidonic acid and the sum of linolenic and icosapentaenoic acids. The first block was received from the control group. The second block presented the results of high intake of oleic acid. In this block the

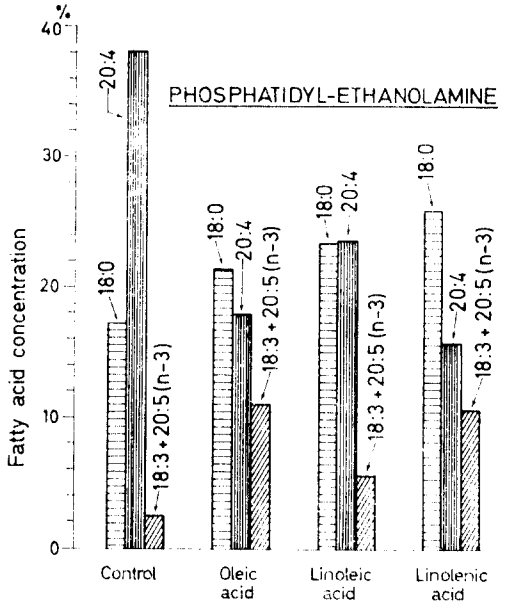


**Fig. 8**: Influence of exogenous fatty acids on the composition of phosphatidyl-ethanolamine.

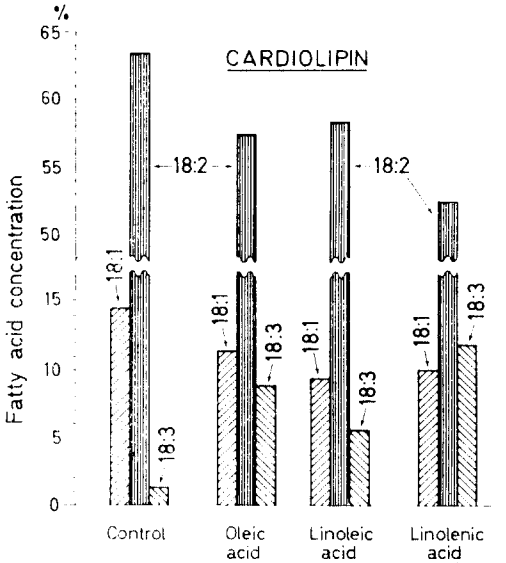


**Fig. 9**: Influence of exogenous fatty acids on the compositon of cardiolipin.

extreme reduction of the concentration of arachidonic acid from 40 to 15% is striking. Under those conditions the concentration of stearic acid, oleic acid and linoleic acid increase slightly. The next block shows the effect of high intake of linoleic acid. The concentration of arachidonic acid becomes a bit higher, but it remains considerably lower than in the control group. This finding is caused by a basic concentration of 20% of linolenic acid in the diet. The lowering effect of this acid exceeds the increasing effect of linoleic acid. In the last block, the influence of feeding big quantities of linolenic acid is demonstrated. The consequence is a low concentration of arachidonic acid, and a further increase of stearic acid in that phospholipid.

It should be emphasized, that oleic acid showed a distinct effect on the composition of the phospholipid. That means, oleic acid is not biologically indifferent, as it was often presumed till now. This observation can also be made by analysing the cardiolipin fraction of the kidnies, which is shown in Fig. 9.

It is well known, that cardiolipin is an important and very active constituent of the mitochondrial membrane. The presentation is the same as in Fig. 8. The observed effects vary from that, seen in phosphatidyl-ethanolamine. The main fatty acid in cardiolipin is linoleic acid. The intake of fat containing about 45% of oleic acid depresses the concentration of linoleic acid in cardiolipin from 60% to less than 20%. The loss is compensated by an increase of stearic and oleic acids. High doses of linoleic acid make an increase of this acid in the cardiolipin fraction. Of interest is the effect of linolenic acid. With respect to the control group, the contents of palmitic and oleic acids have increased. Linoleic acid is reduced. This reduction is compensated by increasing concentrations of linolenic acid and icosatrienoic acid, not included in the graph.

Quite other is the reaction of sphingomyelin,

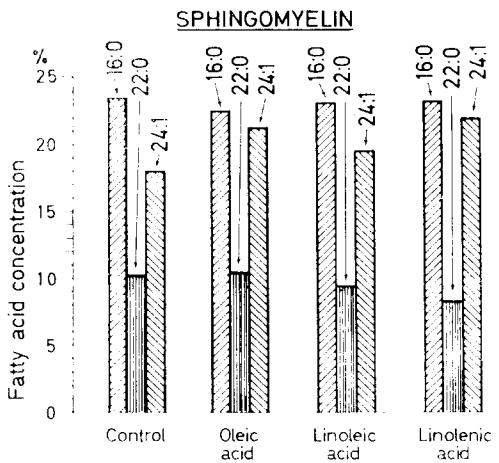


**Fig. 10**: Influence of exogenous fatty acids on the composition of sphingomyelin.

presented in Fig. 10.

Only little variations were observed. Nervonic acid, which is specific for sphingomyelin, was slightly increased by oleic acid as well as by linolenic acid. That an $\omega 3$ fatty acid (lino-lenic acid) affects the concentration of an $\omega 9$ fatty acid (nervonic acid) was surprising.

The variations in the composition of phospholipids are expected to have biological consequeces[2,3]. The degree of unsaturation influences the fluidity of the bilayers in membrane models and the thermal phase transition temperature of the bilayers. Membrane phospholipids are important sources for polyunsaturated fatty acids needed as precursors for the prostaglandin synthesis. And finally, phospholipids are necessary to activate enzyme proteins. A short selcetion of those enzymes is listed in Table II together with the lipids needed as activating "cofactors".

Phosphatidyl-ethanolamine, cardiolipin, phosphatidyl-cholin, and sphingomyelin are needed as co-factors. In some cases also other lipids act as activators. It is a general experience, that all enzymes catalysing reactions of substrates which are insoluble in water need lipids as co-factors.

**Table II: Phospholipids as "co-factors" for enzymes.**

| Protein | Phospholipid |
|---|---|
| Galactosyl-transferase | Phosphatidylethanolamine |
| | Cardiolipin, a.o. |
| Glucosyl-transferase | Phosphatidylcholine |
| 5′-Nucleotidase | Sphingomyeline |
| Cytochrome oxidase | Cardiolipin |
| β-Hydroxybutyrate-dehydrogenase | Phosphatidylcholine |
| ADP:ATP-carrier protein | Phosphatidylcholine |

Despite the variations observed in the fatty acid composition in the phospholipids, the dietary influence on the biological functions of the organism is reduced by a counter-regulation. The degree of unsaturation of a phospholipid can be expressed as "mean number of double bonds per molecule"[4]. Fig. 11 shows the mean numbers of double bonds, determined in the phospholipids from the described feeding experiments. Though the fatty acid composition has been varied in the several feeding blocks, the "mean numbers of double bonds" remain nearly constant, Only higher doses of linolenic acid cause a small increase of the number in cardiolipin, and corresponding a small decrease in

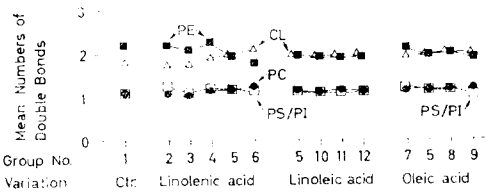


**Fig. 11**: "Mean numbers of double bonds" in phospholipids of kidneys.
PE =Phosphatidyl-ethanolamine
CL =Cardiolipin
PC =Phosphatidyl-choline
PS/PI=Mixture of phosphatidylserine and-inositol

the degree of unsaturation in phosphatidylethanolamine[5].

It is well known and often discussed, that the fat in the diet influences the blood lipids. Often, the effect has been simplified to sentences like:

reduced fat intake reduces triglycerides in blood serum, and

increase of polyunsaturated fatty acids in the diet reduces serum cholesterol levels.

The results of the discussed feeding experiments were quite different from those simplifications[6].

Fig. 12 shows the influence of dietary fatty acids on serum triglycerides. In the first point left the concentration in the low fat control group is given. Higher fat intake increases the triglyceride concentration. But increasing portions of linolenic acid in that fat reduce the triglycerides significantly. Linoleic acid had no significant effect. The last curve shows that oleic acid had a significant decreasing effect on the blood level of triglycerides.

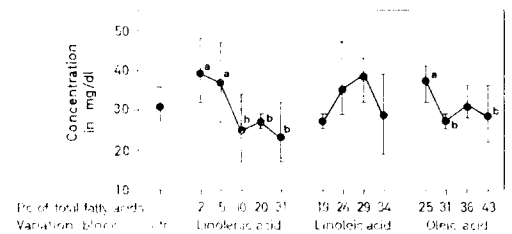


**Fig. 12**: Changes in serum triglyceride content caused by dietary fatty acids.

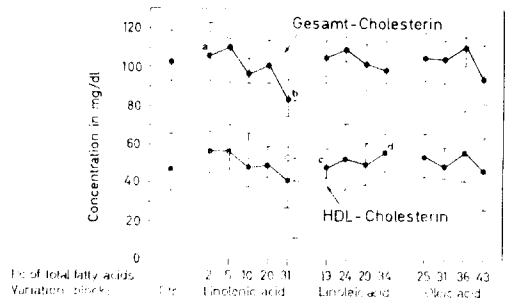


**Fig. 13**: Influence of dietary fat composition on serum cholesterol and high density lipoprotein (HDL) levels.

The influence of the fat composition on the serum cholesterol level is shown in Fig. 13.

In the total cholesterol no change was seen by linoleic acid and by oleic acid. Only high doses of linolenic acid (31% of the fatty acids) reduced the total cholesterol significantly. The HDL-cholesterol was not influenced significantly in the feeding groups with increasing amounts of linolenic acid and oleic acid. But this important cholesterol fraction is significantly increased by linoleic acid.

With respect to prevention of arteriosclerosis the proportion of cholesterol is important, which is transported by the HDL fraction in the serum. The changes in this relationship is represented in Fig. 14.

In the low fat diet the lowest percentage was found. Increasing amounts of linolenic acid reduced the HDL share significantly. Linoleic acid developed an opposite effect. More linoleic acid in the dietary fat increased the HDL cholesterol. Oleic acid had no effect on this relationship.

*Consequences on Prostaglandin Precursors*

It is well known and intensively investigated, that polyunsaturated fatty acids of the $\omega 6$ and partially of the $\omega 3$-families are essential for healthy life and development of the organism[7]. One of their different essential functions is

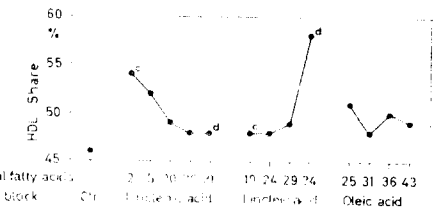


**Fig. 14**: HDL-fraction as percentage of total serum cholesterol.

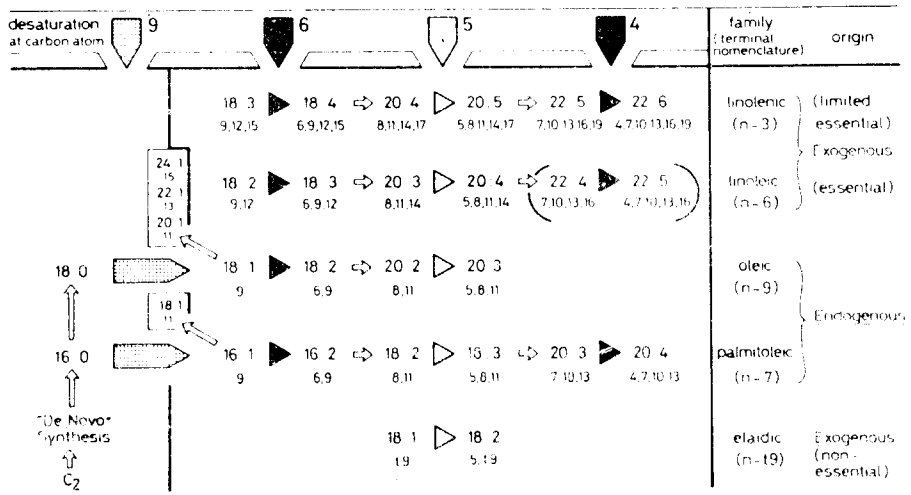


**Fig. 15**: Main pathways of poly unsaturated fatty acid biosynthesis in mammals[11].

their role in prostaglandin production[8,9].

Not the digested fatty acids but their desaturation and elongation products having 20 carbon atoms are the real prostaglandin precursors. Between the 6 fatty acids with 20 carbon atoms registered in Fig. 15 are important the dihomo $\gamma$-linolenic acid, the arachidonic acid and in the $\omega$3-family the icosapentaenoic acid. Besides their effect as precursor for icosanoids it is to mention that other metabolites have steering functions on the enzymes in the prostaglandin synthesis.

The metabolic transformation of the direct precursors into icosanoids is mostly formulated using arachidonic acid as primary substance. That is also the matter in Fig. 16.

This scheme shows the pathway of transformations leading to prostaglandins, prostacyclins and thromboxanes. Starting with arachidonic acid with its 4 double bonds, the prostaglandin family is formed with two double bonds outside the ring system. This family bears the index 2. Analogous reactions occur with dihomo-$\gamma$-linolenic acid, having only 3 double bonds. The result is the icosanoid family with index 1. And icosapentaenoic acid with its 5 double bonds is the mother substance for icosanoids indexed with 3.

The different icosanoids are formed with different reaction speeds. Therefore, a mixture of the 3 precursors lead to different composed mixtures of icosanoids. Furthermore, the activities of the individual prostaglandins are quite different. Schematically linoleic acid is transformed to prostacyclin $PGI_2$ and to thromboxane $T\times A_2$ whereas Linolenic acid led to $PGI_3$ and $T\times A_3$.

Prostacyclin is formed in the wall of blood vessels to prevent the artery against adhesion of blood platelets. Refering to our example, both hormons $PGI_2$ and $PGI_3$ are active. Thromboxanes are factors in the system of platelet aggregation, as you know. $T\times A_2$ is active, whereas $T\times A_3$ is inactive in *in vitro* experiments. *In vivo* no formation of $T\times A_3$ could be obseved.

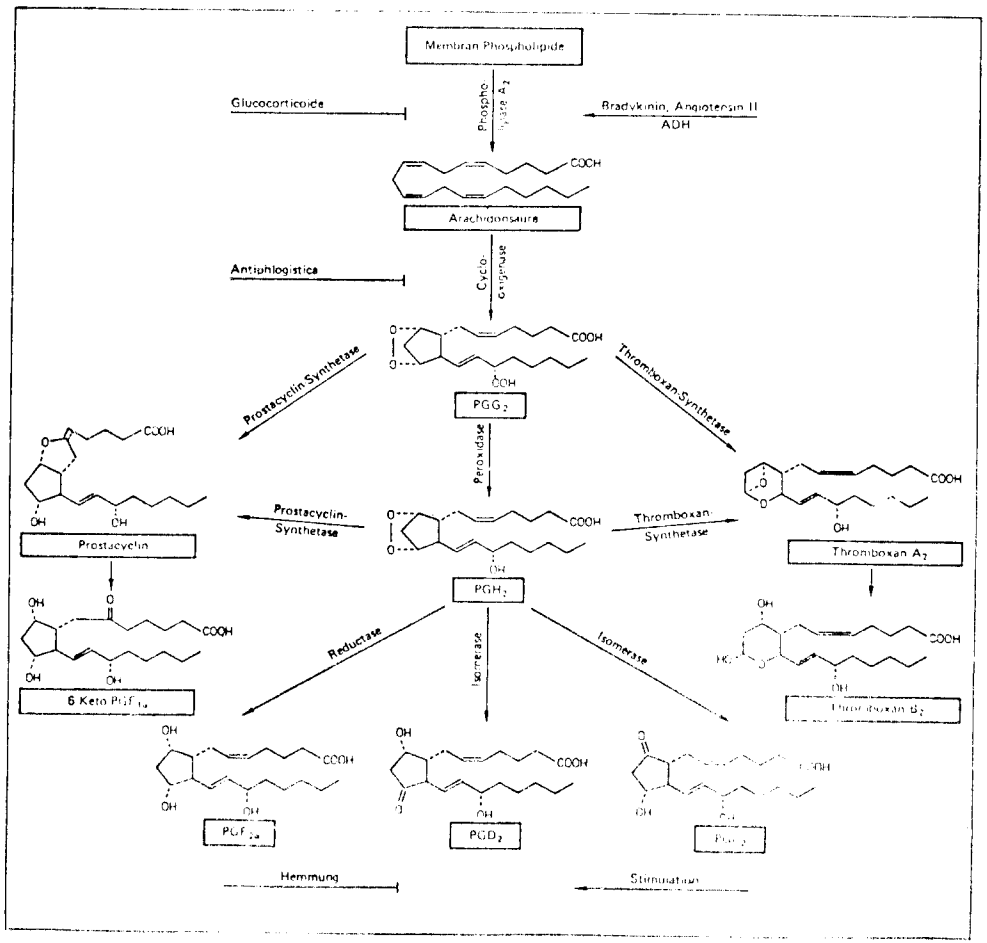


**Fig. 16**: Biochemistry of prostaglandin system.

In healthy organisms $PGI_2$ and $T \times A_2$ are in a balance to prevent arteries against thrombus adhesion and on the other side to prevent the organism against bleeding. If this balance is disturbed tendency towards arteriosclerosis or towards prolonged bleeding occurs. Examples of those imbalances have been observed in man.

The main sources of fatty acids forming icosanoid precursors are the membrane lipids. These phospholipids react with phospholipiase $A_2$, which splits off the fatty acid bound in the 2-position of the phospholipid. The resulting fatty acid mixture formes the substrate for cyclooxygenase initiating the following reaction steps. It was demonstrated that the fatty acids in the diet influence the composition of membrane phospholipids. Followingly, the mixture of fatty acids serving as precursors for prostaglandins is influenced by the composition and the quantity of fat in the diet[10].

Comparing Eskimo to the Danish population it was detected that Eskimo suffer on prolonged bleeding. But they have only one tenth of the rate of heart infarction of the Danish people. The key to this observation was found in the nutrition of both groups of people[12-14] (Table III).

**Table III: Intake of fatty acids per day and caput.**

| Fatty acid family | Greenland-Eskimo | Danes |
|---|---|---|
| ω6-Fatty acids | 5.4g | 10 g |
| ω3-Fatty acids | 13.7g | 2.8g |

Eskimo have a high intake of fish and other marine animals. This causes a daily intake of about 14g of ω3-fatty acids and only 5g of ω6-fatty acids. Danes on the continent eat daily twice the quantity of ω6-fatty acids, and less than 3g of ω3-fatty acids.

It was estabilshed that this difference in the diet causes a significant difference in the mixture of prostacyclin and thromboxane in the blood serum of both populations.

In pharmaceutical research the obstruction of prostaglandin synthesis by anti-inflammatory drugs is prevailing[15]. Direct application of specific prostaglandins failed mostly by their short halb-life time, and/or by side effects. Most recent results in studies with monkeys let expect, that balanced mixtures of prostaglandins may become usable for medication.

perhaps better knowledge of dietary influence on membrane phospholipids may help to steer the prostaglandin synthesis in the tissues, to promote formation of physiological needed icosanoids or to hinder the synthesis of undesirable prostaglandins to prevent chronical diseases[16].

Since several years it is known, that a number of diseases is caused by a surplus of prostaglandins in the tissue[17]. Table IV shows some of those diseases caused by overproduction in the affected tissue.

**Table IV: Surplus of prostaglandins and diseases.**

| |
|---|
| Heart attack |
| Apoplectic stroke |
| Arthritis |
| Dysmenorrhea |
| Asthma |
| Allergy |
| Sun burning |

It is well known, that many drugs to sooth or to cure those diseases, like anti-rheumatic or anti-pyretic drugs,inhibit the prostaglandin synthesis[18,19,20]. A similar effect can be produced by fatty acids in the diet.

In *in vitro* tests with tissue homogenates several fatty acids inhibit the prostaglandin synthesis. In Table V inhibition constants for some fatty acids are listed[21]. Higher concentrations of oleic acid stop the prostaglandin synthesis. More active are ω3-fatty acids. The highest activity was observed in icosapentaenoic and in docosahexaenoic acids. The mode of action of these fatty acids is quite different. For instance, linolenic acid hinders the transformation of linoleic acid into arachidonic acid. Icosapentaenoic acid has been found to hinder the prostaglandin-synthetase-complex.

Furthermore, the relationship between linoleic acid and linolenic acid in the food influences the composition of prostaglandin mixture in the cells and tissues. As it is shown in Fig. 17, the different enzyme complexes transform the precursors into different prostaglandins, having also different effects on the organism[10].

In Fig. 17 the formation of $PGD_2$, $PGE_3$ and $PGF_{2\alpha}$ is shown. The physiological activity and the biological effect of these different prostaglandins is quite different. Therefore, an influence on the ratio of synthesis of the diffe-

**Table V: Inhibition constants of fatty acids on prostaglandin synthesis.**

| | | |
|---|---|---|
| 18 : 1 | ω9 | 22 μMol |
| 18 : 3 | ω3 | 15 μMol |
| 20 : 3 | ω3 | 6 μMol |
| 20 : 5 | ω3 | 2.5μMol |
| 22 : 6 | ω3 | 1.7μMol |

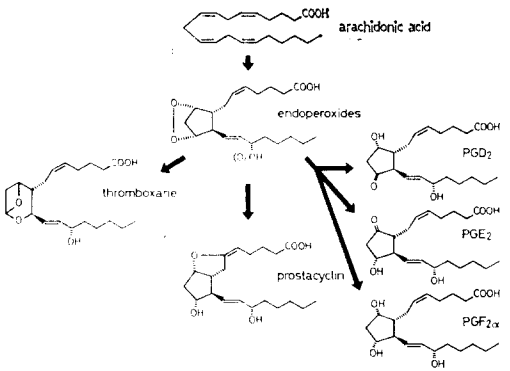


**Fig. 17**: Formation and structures of the main prostaglandins.

rent prostaglandins influences also the biological reactions. This influence can be realized by the dietary fat. It has been found that the concentration of linoleic acid in the nutrition influe nces the relationship between $PGE_2$ and $PGF_{2\alpha}$ in the human tissuse. More linoleic acid causes more $PGE_2$ and less $PGF_{2\alpha}$. Reduction of linoleic acid in the diet reverse the relationship of these two prostaglandins. In mixtures of linoleic and linolenic acids the synthesis of $PGE_2$ is reduced, whereas the concentration of $PGF_{2\alpha}$ is unchanged. These are first findings on the influence of linoleic and linolenic acids on the formation of prostaglandins.

*Final Remarks*

In the last few years, many important obserrvations have been made in test animal as well as in man. More recent results have changed our mind on an optimal composition of dietary fat. But to find definit solutions for practical advise for human nutrition, further intensive investigations are necessary. Those studies must take in consideration the effect of trans isomers on prostaglandin-synthetase-complex as well as the direct physiological activities of some polyunsaturated fatty acids on membrane fluidity, platelet aggregation— like icosapentaenoic acid[22]—, heart rhythm—influenced by docosahexaenoic acid[23]—, or brain and eye functions, which need linolenic acid[24,25],

The reviewed results are steps of a worldwide activity on this difficult and long way of research.

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