ROLES OF UNSATURATED FATTY ACIDS (ESPECIALLY OMEGA-3 FATTY ACIDS) IN THE BRAIN AT VARIOUS AGES AND DURING AGEING

J.M. BOURRE

Member of the French Academy of Medicine. INSERM Research Director. Director of Unit U26 Neuropharmaco-nutrition. Hôpital Fernand Widal, 200 rue du Faubourg Saint Denis. 75745 Paris cedex 10. Mail : jean-marie.bourre@fwidal.inserm.fr, Téléphone : 01 40 05 43 39, Télécopie : 01 40 34 40 64

Abstract: *Among various organs, in the brain, the fatty acids most extensively studied are omega-3 fatty acids. Alpha-linolenic acid (18:3ω3) deficiency alters the structure and function of membranes and induces minor cerebral dysfunctions, as demonstrated in animal models and subsequently in human infants. Even though the brain is materially an organ like any other, that is to say elaborated from substances present in the diet (sometimes exclusively), for long it was not accepted that food can have an influence on brain structure, and thus on its function. Lipids, and especially omega-3 fatty acids, provided the first coherent experimental demonstration of the effect of diet (nutrients) on the structure and function of the brain. In fact the brain, after adipose tissue, is the organ richest in lipids, whose only role is to participate in membrane structure. First it was shown that the differentiation and functioning of cultured brain cells requires not only alpha-linolenic acid (the major component of the omega-3, ω3 family), but also the very long omega-3 and omega-6 carbon chains (1). It was then demonstrated that alpha-linolenic acid deficiency alters the course of brain development, perturbs the composition and physicochemical properties of brain cell membranes, neurones, oligodendrocytes, and astrocytes (2). This leads to physicochemical modifications, induces biochemical and physiological perturbations, and results in neurosensory and behavioural upset (3). Consequently, the nature of polyunsaturated fatty acids (in particular omega-3) present in formula milks for infants (premature and term) conditions the visual and cerebral abilities, including intellectual. Moreover,*

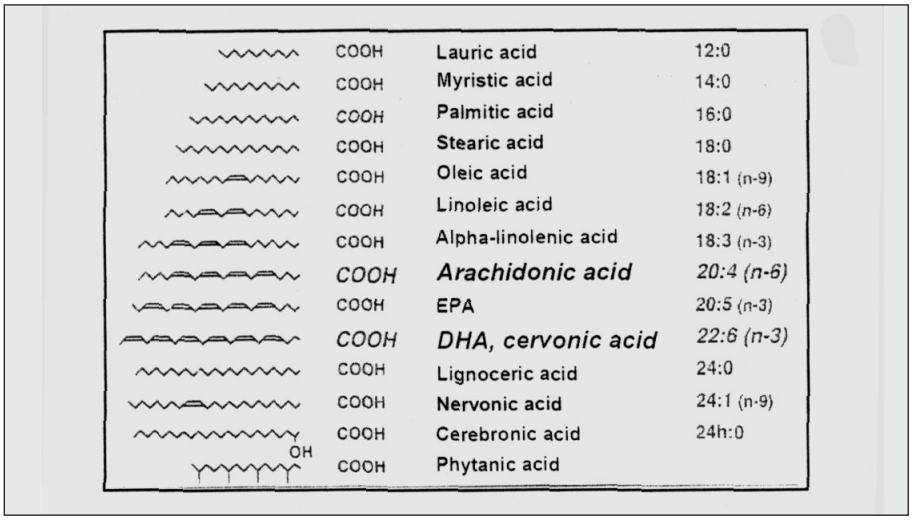
dietary omega-3 fatty acids are certainly involved in the prevention of some aspects of cardiovascular disease (including at the level of cerebral vascularization), and in some neuropsychiatric disorders, particularly depression, as well as in dementia, notably Alzheimer's disease. Recent results have shown that dietary alpha-linolenic acid deficiency induces more marked abnormalities in certain cerebral structures than in others, as the frontal cortex and pituitary gland are more severely affected. These selective lesions are accompanied by behavioural disorders more particularly affecting certain tests (habituation, adaptation to new situations). Biochemical and behavioural abnormalities are partially reversed by a dietary phospholipid supplement, especially omega-3-rich egg yolk extracts or pig brain. A dose-effect study showed that animal phospholipids are more effective than plant phospholipids to reverse the consequences of alpha-linolenic acid deficiency, partly because they provide very long preformed chains. Alpha-linolenic acid deficiency decreases the perception of pleasure, by slightly altering the efficacy of sensory organs and by affecting certain cerebral structures. Age-related impairment of hearing, vision and smell is due to both decreased efficacy of the parts of the brain concerned and disorders of sensory receptors, particularly of the inner ear or retina. For example, a given level of perception of a sweet taste requires a larger quantity of sugar in subjects with alpha-linolenic acid deficiency. In view of occidental eating habits, as omega-6 fatty acid deficiency has never been observed, its impact on the brain has not been studied. In contrast, omega-9 fatty acid deficiency, specifically oleic acid deficiency, induces a reduction of this fatty acid in many tissues, except the brain (but the sciatic nerve is affected). This fatty acid is therefore not synthesized in sufficient quantities, at least during pregnancy-lactation, implying a need for dietary intake. It must be remembered that organization of the neurons is almost complete several weeks before birth, and that these neurons remain for the subject's life time. Consequently, any disturbance of these neurons, an alteration of their connections, and impaired turnover of their constituents at any stage of life, will tend to accelerate ageing. The enzymatic activities of synthesis of long-chain polyunsaturated fatty acids from linoleic and alpha-linolenic acids are very limited in the brain: this organ therefore depends on an exogenous supply. Consequently, fatty acids that are essential for the brain are arachidonic acid and cervonic acid, derived from the diet, unless they are synthesized by the liver from linoleic acid and alpha-linolenic acid. The age-related reduction of hepatic desaturase activities (which participate in the synthesis of long chains, together with elongases) can impair turnover of cerebral membranes. In many structures, especially in the frontal cortex, a reduction of cervonic and arachidonic acids is observed during ageing, predominantly associated with a reduction of phosphatidylethanolamines (mainly in the form of plasmalogens). Peroxisomal oxidation of polyunsaturated fatty acids decreases in the brain during ageing, participating in decreased turnover of membrane fatty acids, which are also less effectively protected against peroxidation by free radicals.

Key words: *Brain, fatty acids, omega-3, ageing.*

INTRODUCTION

The brain is composed of three main types of cells: neurons and glial cells, mainly astrocytes (having classic functions of support and segregation of neuron, regulation of neuron commmunication, neurosecretion, modulating synaptic plasticity and activity) and oligodendrocytes (myelin sythesizing cells). Other cells also have important roles, such as endothelial cells of cerebral capillaries. Neurons account for only about 1/4 of the weight of the brain. Nervous tissue has the highest lipid concentration, immediately after adipose tissue. These fatty acids, almost all structural and not energetic, participate directly in the architecture and therefore in the functioning of cerebral cell membranes, including those which ensure compartmentalization of the cell and individualization of its organelles. Life is strictly impossible in the absence of the two essential fatty acids because cell membranes can no longer be formed or maintained. At one time, these essential fatty acids were called "vitamin F". The cell membrane – composed of large quantities of phospholipids – ensures the individuality of cells and acts as a support for a large number of specific physiological activities. The fatty acid composition of a phospholipid is specific to the membrane (and cell) to which it belongs.

Figure 1
Nomenclature of the main fatty acids



Fatty acids can be classified into two categories: non-essential fatty acids that are synthesized by all organs, including the brain (saturated or monounsaturated, possibly alpha-hydroxylated fatty acids), and essential fatty acids that must be provided in the diet. In fact, cerebral membranes phospholipids are not composed of the dietary precursors, linoleic acid and alpha-linolenic acid, but their longer chain and more unsaturated derivatives; however minute amount of free linoleic and free alpha-linolenic acid are found.

An average of one in three fatty acids in the nervous system is polyunsaturated. Position 2 of phospholipids is generally occupied by a polyunsaturated fatty acid, which is usually 20:4ω6 (arachidonic acid), 22:4ω6 (adrenic acid), 22:5ω3 and especially 22:6ω3 (DHA, cervonic acid). Polyunsaturated fatty acids of the omega-3 series have very special roles in cell membranes, especially in the nervous system: all brain cells and organelles contain high levels of these fatty acids, but they are not present in sufficient quantities in modern occidental (including French) diets.

The importance of dietary omega-3 polyunsaturated fatty acids is well known, as these compounds decrease the incidence of cardiovascular disease and constitute precursors of biologically active derivatives (such as prostaglandins and leukotrienes). However, their structural role in membranes, including cerebral membranes, is also qualitatively and quantitatively very important. Among other roles, fatty acids control the composition of membranes and therefore their fluidity and consequently their enzymatic activities, binding between molecules and receptors, cellular interactions, and nutrient transport.

First it was shown that the differentiation and functioning of cultured brain cells requires not only alpha-linolenic acid (the major component of the omega-3, omega-3 family), but also the very long omega-3 and omega-6 carbon chains [1]. The following studies demonstrating the relationship between the effect of a nutrient and the structure and function of the brain were based on alpha-linolenic acid. A discovery in 1984 demonstrated that alpha-linolenic acid deficiency induces abnormalities of the composition of the various cell types and organelles of the nervous system: neurons, astrocytes, oligodendrocytes, myelin, nerve endings, endoplasmic reticulum [2]. These subjects present a very marked cervonic acid deficiency, which is generally compensated by an excess 22:5ω6 (fatty acids described by Galli [4]. The total quantity of polyunsaturated fatty acids is therefore relatively normal; saturated and monounsaturated fatty acids are virtually not affected. Dietary alpha-linolenic acid is preserved in nervous tissues (and its very-long-chain derivatives are reutilized), as a 21-fold decrease in dietary intake results, at worst, in only a 5-fold decrease in alpha-linolenic acid levels in the various organs examined, and only a twofold decrease in

neurons.

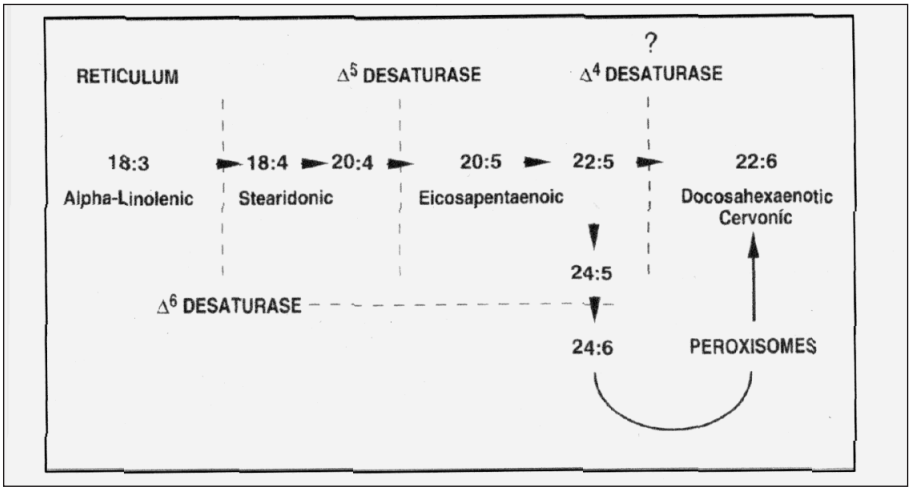
It was subsequently demonstrated, in 1989, in a study of the biochemistry, physicochemistry, toxicology, electrophysiology and behaviour in the same series of animals, that these fatty acids can control certain electrophysiological parameters, and certain higher functions (learning). A reduction of these fatty acids induces an alteration of membrane functioning (enzyme, receptor, transporter activities), and an increased susceptibility of these membranes to aggression. A dose-effect relationship has been demonstrated between the quantity of dietary alpha-linolenic acid and the DHA content of cerebral structures [3], in young as well as adult animals [5]. The rate of recovery after correction of the deficiency is very slow [6, 7], including in the cerebral microcirculation [8]. These results have been confirmed many times on many different models [9, 10]. Brainfood have been documented in some books [11, 12].

Simultaneous linoleic acid and alpha-linolenic acid deficiency is obviously incompatible with life, as it alters the fatty acid composition of all organs, including the brain [4]. In the course of evolution, the dietary acquisition of DHA largely contributed to the development of the human brain [13].

Studies can only be conducted on animal models, as it is obviously impossible to study the effects of nutrients on the human brain. Animal studies provide certain leads that can sometimes be partially validated in man, but they usually only provide confirmation.

This review will analyse most of the studies concerning unsaturated fatty acids and ageing. However, after a brief reminder of the general relationships between fatty acids of the three families and the brain, this review will only present recent data, i.e. studies conducted since 2000 until the end of January 2003. Only results concerning mammals will be presented, while data derived from birds (particularly hens, eggs, and possibly the chicks derived from these eggs) were not taken into account. Schematically, the very great majority of the published results concern omega-3 fatty acids, and only a very small minority of studies are strictly devoted to omega-6 fatty acids; when omega-6 fatty acids are mentioned, it is only in reference to omega-3 fatty acids. Several interesting studies have been published on omega-9 fatty acids, particularly oleic acid.

Figure 2
Anabolism of long-chain polyunsaturated fatty acids from precursors, essential fatty acids (linoleic acid and alpha-linolenic acid).



NOMENCLATURE

Fats are mainly composed of molecules called triglycerides, in turn composed of fatty acids. The type of fatty acid determines the nutritional characteristics of each type of fat. "Saturated" fats are predominantly composed of saturated fatty acids; monounsaturated fats are predominantly composed of monounsaturated fatty acids (mainly oleic acid) and polyunsaturated fats contain useful quantities of polyunsaturated fatty acids. Two polyunsaturated fatty acids are essential, i.e. mammals, and therefore man, are unable to synthesize them or even transform them from one to the other. These fatty acids must therefore be supplied in the diet. Before identification of their chemical structure, they were grouped under the term "vitamin F". These essential fatty acids are called linoleic acid and alpha-linolenic acid, and each one constitutes the head of two families of fatty acids called ω6 (omega-6) and ω3 (omega-3) or (n-6) and (n-3) according to chemical nomenclature. Chemically, it would be more accurate to speak of polyethylene chains rather than polyunsaturated chains. The head of the omega-3 family is therefore alpha-linolenic acid. Its derivatives are timnodonic acid (alias eicosapentaenoic acid (EPA), 22:5ω3), which participates in the pharmacological effect of fish oil in the context of prevention and treatment of cardiovascular disease, and cervonic acid (alias docosahexaenoic acid (DHA), 22:6ω3), as the brain is the living structure, which contains the greatest quantities of this fatty acid, which explains why

it was discovered in this organ. The frontal brain, specific to man, is the region of the brain with the highest levels of DHA. All fatty acids in the omega-3 family share a common characteristic: the first unsaturated bond, corresponding to a double chemical bond, is always situated on the 3rd carbon from the metabolically non-reactive methyl end of the chain. This facilitates description, as it is unnecessary to decline all of the names of all fatty acids of the family, presenting double bonds at different points along the carbon chain when counting from the biochemically reactive carboxyl end (according to chemical nomenclature) that undergoes various modifications.

OMEGA-3 FATTY ACIDS

Analysis of the fatty acid composition of total phospholipids of 11 regions of the murine brain shows that the level of 22:6ω3, under normal conditions, is significantly higher in the frontal cortex. Alpha-linolenic acid deficiency does not affect all cerebral structures to the same degree: the pituitary gland, frontal cortex and corpus striatum are the structures most severely affected, with an approximate 40% reduction of 22:6ω3. An egg yolk or pig brain phospholipid supplement can restore a normal fatty acid composition in all regions of the brain, except for the frontal cortex. There is therefore a regional distribution of fatty acids in the brain and the impact of a fatty acid deficiency is consequently "region-specific" [14].

Under conditions of deficiency, omega-3 fatty acids are preserved and reutilized by recycling mediated by deacylation and reacylation reactions, which is decreased by only 30% to 70%, while transfer between the blood and the brain is reduced 40-fold [15], which explains the 50% DHA deficiency initially observed in neurons [1].

Alpha-linolenic acid deficiency induces a reduction of DHA in the hippocampus, associated with a reduction of the size, but not the number of neurons [16], and a specific reduction of omega-3 fatty acids associated with a reduction of a particular phospholipid, phosphatidylserine [17]. In elderly rats, administration of fish oil increases the transcription of transthyretin in this structure [18] and decreases NGF ("nerve growth factor") (Ikemoto et al., 2000). Inhibition of production of the second messenger controlled by protein-kinase constitutes a target for omega-3 fatty acids, at least in vitro [19].

Possibilities of biochemical and behavioural recovery

The dietary use omega-3 alone is unsatisfactory, as a diet enriched in fish oil enhances alertness and acquisition of learning in young mice, but

decreases motor activity and learning in elderly mice [20].

Exploratory activity is significantly reduced in omega-3 deficient mice. On the elevated plus-maze (a test which measures anxiety), the time spent in the open arms of the apparatus was significantly lower in omega-3 deficient mice than in controls. The use of the learning protocol on the maze showed that omega-3 deficiency impaired learning. A phospholipid supplement (in this case eggs enriched with omega-3, but also containing omega-6) reversed the biochemical and behavioural alterations induced by omega-3 polyunsaturated fatty acid deficiency in mice, as exploratory activity and learning were totally restored after egg or pig brain phospholipid supplementation, while the level of anxiety was not restored to the same level as that of the controls. Recovery was therefore incomplete [21].

There is a time lag between incorporation of fatty acids in the brain and improvement of learning performances [22]. Note that egg extracts enriched in omega-3 and omega-6 have been used for several years to prepare special milk formulas and that pig brain phospholipids have been used in small-for-dates infants [23].

A DHA-rich phospholipid supplement improves behaviour, learning and visual function in control elderly mice and mice with omega-3 polyunsaturated fatty acid deficiency [24]. Pure DHA (in the form of ethyl ester) provides similar results [25].

An intra-amniotic injection in oméga-3 fatty acid deficient animals corrects omega-3 fatty acid deficiency of the foetal brain in 24 hours [26].

In human, omega-3 fatty acids could reduce cognitive decline and the risk of dementia including the Alzheimer type [27, 28] and have been involved in schizophrenia [29, 30] and in depression [31] as well as in neurologically disabled children [32].

Dose-effects: triglycerides or phospholipids?

Alpha-linolenic acid is probably elongated and desaturated by the liver into longer chains that actually constitute the essential fatty acids for the brain, as initially discovered in nerve cell cultures, which only differentiate, multiply, bind and release neurotransmitters when the culture medium contains 20:4ω6 and 22:6ω3; but not in the presence of 18:2ω6 and 18:3ω3 [1]. A recent dose-effect study showed that egg or pig brain phospholipids are better sources of polyunsaturated fatty acids than soybean phospholipids, as they directly provide long-chain polyunsaturated fatty acids [33]. Similar results have been observed with omega-6 fatty acids [34].

Neurotransmission, signalling, transport

Alpha-linolenic acid deficiency results in disorders of monoaminergic neurotransmission in the rat frontal cortex, that could be linked to the observed behavioural and cognitive deficits. There is obviously a relationship between polyunsaturated fatty acids, neurotransmission and behaviour [35, 36], but neither the density nor the function of dopamine transporters are affected [37]. In alpha-linolenic acid deficient animals, the disorder of dopaminergic neurotransmission (in the prefrontal cortex, among others) is only partially reversed after correction of the dietary deficiency [38].

A PET study in conscious monkeys showed that modulation of cholinergic neurotransmission by DHA not only involves cerebral structures, but also cerebral blood flow [39].

In terms of signalling, intracellular and intercellular relationships may be affected by omega-3 fatty acid deficiency, which decreases accumulation of phosphatidylserine that can induce modifications of signal contents [40].

A very important finding is that omega-3 fatty acid deficiency can modify the energy metabolism of the brain by altering glucose transport [41].

Electrophysiological studies show that alpha-linolenic acid deficiency induces electroencephalographic changes [36].

Sense organs: vision, hearing, smell and taste

Vision is dependent on the nature of dietary fatty acids. The retina, part of the central nervous system, is one of the tissues with the highest levels of omega-3 polyunsaturated fatty acids. Omega-3 fatty acid deficiency induces modifications of the distribution of membrane fatty acids of the retina associated with alterations of the amplitude of "a" and "b" waves on the electroretinogram [3].

In oméga-3 fatty acid deficient mice, phospholipid supplementation induces a significant increase in the amplitude of the "b" wave in both controls and deficient mice. It also restores a normal fatty acid composition of the retina [24]. In fact, DHA plays an important role in vision, involving the retina and brain: photoreceptors, neurotransmission, activation of rhodopsin, development of cones and rods, neuronal synapses and maturation of cerebral structures [42].

As many behavioural tests directly or indirectly depend on vision, it is fundamental to observe that learning deficits in alpha-linolenic acid deficient mice are not due to visual impairment [43].

The concentrations of DHA-rich phospholipids in the retina decrease

during ageing [44].

Similar results have been reported for smell: alteration of tests assessing the sense of smell is not due to a reduction of olfactory function per se, but to an alteration of cerebral structures [45].

For the first time, it has been shown that omega-3 fatty acid deficiency alters hearing, particularly the cerebral response to auditory stimuli. It also induces premature or more accelerated ageing of the auditory nervous system. Fatty acids affect the efficacy of sensory receptors, but also cerebral receptor structures [46]. Maternal dietary docosahexaenoic acid content affects the rat pup auditory system [47]. Phosphatidylcholine (lecithin) could preserve mitochondrial function of the cochlea, and consequently protect against age-related hearing loss [48].

Omega-3 fatty acid deficiency alters taste. For example, a given level of perception of a sweet taste requires a larger quantity of sugar in animals with alpha-linolenic acid deficiency [49].

Omega-3 fatty acids in psychiatry

Omega-3 fatty acids may prove to be efficacious in a number of psychiatric disorders [50]. Mood disorders have been asociated with diminished omega-3 fatty acid concentrations. Reduced DHA levels in adipose tissue are related to depression [51]. Plasma fatty acid composition and depression are associated in the elderly [52]. Clinical data are not clear regarding the treatment of major depression. Abnormal phospholipid turnover has been described in schizophrenia [29]; specific treatment with EPA would be useful in schizophrenia [30], and also in depression [31]. Double blind treatments have been efficacious in bipolar disorders. Omega-3 fatty acid are usefull in prevention and even treatment of dementia. Overall, in man, omega-3 fatty acids could reduce cognitive decline and the risk of dementia [27]. In various types of dementia, including the Alzheimer type, low plasma levels of omega-3 fatty acids (including in DHA) constitute a risk factor for these diseases [28]. Decreased level of plasma DHA is a risk factor for cognitive impairment and/or dementia, including alzheimer disease [28, 53]. For instance, patients eating fish or seafood (rich in omega-3 faty acids) at least once a week have a significant lower risk of being diagnosed as having dementia in the seven subsequent years [54]. In very old men, linoleic acid intake is positively associated with cognitive impairment and high fish consumption inversely asociated with cognitive kimpairment [55].

In another field, neurologically disabled children absorb insufficient quantities of omega-3 fatty acids, as reflected by the presence of serum

markers of omega-3 deficiency, 20:3ω9 and 22:5ω6, which interferes with effective renewal of their already damaged cerebral structures [32].

OMEGA-6 FATTY ACIDS

Specific linoleic acid deficiency does not appear to occur in man, as, fortunately, apart from exceptional cases of artificial diet lasting several months, it would be difficult not to absorb linoleic acid, as this fatty acid is present in variable quantities in the majority of foods. Selective, serious linoleic acid deficiency has therefore never been observed in man, but perhaps because sufficiently detailed investigations have not been conducted.

Almost all of the studies listed in the references did not deal directly with omega-6 fatty acids, but with their relationships with omega-3 fatty acids. Only the minimum dietary requirements have been determined in animals [56]. The effect of an increase of linoleic acid on tissue concentration of cevonic acid and consequentely on alpha-linolenic requirement have been documented [57]. In baboons, 22:4ω6 is mainly formed from arachidonic acid (20:4ω6). A reduction of the arachidonic acid content is observed during ageing, related to glutamate receptors [58].

Recovery after ω3 fatty acid deficiency is only possible if w6 fatty acids do not induce excessive competition [59].

Oméga-6 and omega-3 fatty acids modulate neurotransmitter metabolism, at least in piglets [60] and, in rats, they participate in the hippocampus receptor density, which could account for the effects of these fatty acids on memory [61]. Competition between omega-3 and omega-6 fatty acids does not concern recycling, but elongation and desaturation reactions [62].

In mice, maternal exposure to a diet very rich in oméga-6 fatty acids during pregnancy induces increased alcohol consumption in females of the litter [63], in line with observations showing that alcohol interferes with the fatty acids of nerve endings [64].

Consumption of foods with a well defined omega-3/omega-6 ratio is effective against various components of stress [65].

Indeed, the ration omega-6/omega-3 essential fatty acids is very important, a lower ration is more desirable in reducing the risk of many chronic diseases of high prevalence in Western societies, as well as in developing countries [66].

OMEGA-9 FATTY ACIDS: OLEIC ACID

The nutritional value of oleic acid in the context of a balanced diet has been the subject of a number of studies, with particular emphasis on the cardiovascular system. However, very recent research has demonstrated that this fatty acid is also important for the brain [67]. In the brain, omega-9 fatty acids consist of oleic acid, but also very large quantities of longer-chain derivatives, mainly 24:1, especially in the myelin sheath.

Commercial vegetable oils cannot be used to precisely determine the effect of the presence and the concentration of oleic acid in the diet on the fatty acid composition of various organs, as they always contain oleic acid. Sufficiently large quantities of triglycerides to be compatible with nutritional investigations were therefore synthesized chemically and enzymatically; they were composed of either oleic acid, alpha-linolenic acid, or linoleic acid. Globally, in rats, dietary oleic acid deficiency leads to a reduction of the oleic acid concentration in many organs, including the sciatic nerve, but not in the brain. In many organs, endogenous synthesis therefore does not compensate for the absence of oleic acid in food [68]. This fatty acid is therefore partially essential, especially during pregnancy and lactation, at least in rats.

The absence of modifications of the 18:1ω9 concentration of cerebral structures according to the oleic acid content of the diet raises several hypotheses. Either the nervous system selectively binds oleic acid, suggesting the possibility of specific, active transport mechanisms across the blood-brain barrier, or it is able to synthesize all of the oleic acid that it needs, independently of its presence in the diet [67], as a stearyl desaturase has been demonstrated to be active in the brain [69]. In mice presenting signs of accelerated ageing, a reduction of this delta-9-desaturase is detected in the hippocampus, which could account for the observed behavioural disturbances [70].

Free fatty acids (including oleic acid) were assayed in the cerebrospinal fluid of a large series of patients [71]. An oleic acid derivative, oleamide, modulates sleep [72] and reduces apoptosis of cerebellar neurons [73].

AGEING AND FATTY ACID COMPOSITION

A reduction of arachidonic acid incorporation in the brain and a reduction of its turnover are observed during ageing [74]. Indeed, myelin membrane in extremely rich in lipids [75], consequently nutrition play an important role in myelination, and severe malnutrtion and essential fatty acid deficiency cause severe hypomyelination [76] and myelin lipid turn-over is

affected during aging [77].

A recent study examined the composition of the human cortex between the ages of 2 years and 88 years [78]. Globally, DHA and monounsaturated fatty acid concentrations increase up until the age of 18 years. During ageing, the levels of polyunsaturated fatty acids, especially arachidonic acid, decrease, while the level of alpha-linolenic acid increases. The polyunsaturated fatty acid content of phosphatidylethanolamine is markedly decreased in Alzheimer's disease [79].

The rat cortex and hippocampus present major changes in their polyunsaturated fatty acid composition, especially affecting the DHA content of phosphatidylethanolamine plasmalogens [80], associated with an alteration of their participation in membrane structures resulting in a reduction of cognitive performances, their participation in neurotransmission and also their antioxidant role during ageing [81].

Globally, during ageing, a reduction of the 20:4ω6, 22:4wω6 and 22:6ω3 concentration is observed in the cortex and cerebellum, associated with an increase in the 18:1ω9 and 20:1ω9 concentrations, mainly in phosphatidylethanolamines and phosphatidylserines [82, 83]. These defects can be corrected by an appropriate diet [84, 85]. A modification of the exchanges of choline and serine bases is also observed during ageing [86]. The microsomal synthesis of phosphatidylethanolamines and phosphatidylserines is decreased during ageing [87]. Another important finding is that phosphatidylserine decarboxylase decreases during ageing, reducing the production of phosphatidylethanolamine [88].

In the hippocampus of ageing rats, dietary alpha-linolenic acid deficiency induces a selective reduction of phosphatidylserine associated with increased MAO-B activity, but has no effect on the serotonin and noradrenaline contents [89].

An increase in the concentration of pro-inflammatory cytokine (interleukin-1-beta) is observed in the brain during ageing [90], which may be responsible for a certain degree of deterioration of certain cellular functions, especially as binding of interleukin-1 to its receptor inhibits the release of glutamate in hippocampal nerve endings of young rats, but not in ageing rats [91].

The reduction of cerebral glucose levels induces modifications of cerebral metabolism, resulting in peroxidation in ageing rats [92].

Turnover of phospholipids (especially phosphatidylcholine and phosphatidylethanolamine) and cholesterol in synaptic membranes is decreased during ageing [93]. The lipid composition of mitochondria present in synapses is also affected, especially their linoleic acid content [94].

The increased cholesterol content of cerebral membranes induces an

increased physical rigidity of these membranes, inducing functional disturbances; membrane fluidity can be restored by a carefully defined polyunsaturated fatty acid supplement [65]; the optimal ratio between omega-6 fatty acids and omega-3 fatty acids is 5:1. In fact, despite intense research on cholesterol, its metabolism in central nervous system and its role in neuronal development and function are not well understood [95]. A link has been proposed between cholesterol and Alzheimer disease [96]. For instance, cholesterol deficiency increases the vulnerablity of hippocampal glia in pirmlary culture to glutamate induced exitotoxicity [97]. It is postulated that during development, neurons reduce cholesterol synthesis and import cholesterol from astrocytes via lipoproteins. Consequently, neurons use glia-derived cholesterol to form synapses [98].

AGEING AND DESATURASE ACTIVITIES

The essential fatty acids for the brain are arachidonic acid and cervonic acid, which are either provided in the diet or are synthesized by the liver from linoleic acid and alpha-linolenic acid. Consequently, the effects of ageing on desaturases (which, together with elongases, participate in the synthesis of long-chain fatty acids) can alter the turnover of cerebral membranes. Changes in hepatic desaturase activities during ageing vary according to the species: they are slightly modified [99, 100] or remain unchanged [101] in rats, and are decreased by one half in mice [102]. This reduction is not observed in alpha-linolenic acid deficient ageing animals [103], which probably allows better preservation of the few remaining omega-3 fatty acids. The specific activity of enzyme, but also the total desaturase capacity of the whole liver must be taken into account [104].

The reduction of delta-6-desaturase activity can be compensated by the addition of gamma-linolenic acid to the diet [105], which results in an increase in delta-6-desaturase kinetic parameters (Vm) for linoleic acid and alpha-linolenic acid in ageing animals [106]. Blackcurrant seed oil contains stearidonic acid (18:4ω3) [107] and beneficial effects on health have been observed in man [108].

Hepatic desaturase activities depend on a number of factors, especially hormonal factors and vitamin B6 [109]; hypertension can also accelerate the ageing process [110]. The combination of vitamin B12 and phosphatidylcholine appears to attenuate the age-related learning deficit, at least in a murine model of accelerated ageing [111]. In Alzheimer's disease, modifications of the cerebral fatty acid composition have been correlated with alterations of desaturase activities [112].

All mechanisms involved in the production and activity of desaturases

can be influenced by the nature of membrane fatty acids. For example, the activity of an enzyme of the nuclear membrane of hepatocytes is dependent on the presence of w3 fatty acids [113].

The fatty acid composition of human adipose tissue is generally altered during ageing, sometimes independently of the composition of the diet [114].

AGEING AND PEROXISOMAL ACTIVITIES

Peroxisomes participate in oxidation of long-chain fatty acids, but they are also involved in the synthesis of very-long-chain polyunsaturated fatty acids, as, in the absence of delta-4 desaturase (which would have transformed 22:5ω3 into 22:6ω3), 22:5ω3 are elongated into 24:5ω3 in the endoplasmic reticulum and then desaturated by a delta-6-desaturase into 24:6ω3, which is then transformed into 22:6ω3 in peroxisomes [115] (Figure 2).

Peroxisomal oxidation of polyunsaturated fatty acids in the brain decreases during ageing [116].

TRANS FATTY ACIDS

As these fatty acids are non-physiological, it is reasonable to suppose that their incorporation into membranes would interfere with the functioning of these membranes, possibly accelerating the ageing process. Their harmful effect on foetal and child development has been suspected [117], especially as the levels of these fatty acids are equivalent in maternal and foetal plasma, indicating permeability of the placenta to these compounds [118]. Trans fatty acids are known to alter cholinesterases in various organs, including the brain [119].

The trans isomer of oleic acid is incorporated into the brain [120]. In mice, the presence of this trans fatty acid in the diet, but associated with a borderline essential fatty acid deficiency, only has a limited effect on cerebral development, but it alters behavioural tests [121].

Trans polyunsaturated fatty acids are incorporated into the brain [122], in mitochondria and microsomes [123], in various cerebral structures, including microvessels, nerve endings and the retina, which contain the highest concentrations, twice the levels observed in myelin and the sciatic nerve. Alpha-linolenic acid deficient animals incorporate twice as much trans polyunsaturated fatty acids [124]; however, the brain appears to be relatively protected [125], at least in animal models.

Trans monounsaturated fatty acids must be distinguished from trans

polyunsaturated fatty acids. One trans polyunsaturated fatty acid, CLA (conjugated linoleic acid), presenting important favourable physiological effects, can be integrated into phospholipids, but only to a limited extent in the brain [126], less than in adipose tissue, muscle, liver and kidneys [127]. However, the effects of CLA on cerebral ageing have not yet been studied.

The incorporation of trans fatty acids modifies the level of monoamines in the cerebral cortex; this effect is reversible for the cortex, but not for the hippocampus [128].

Although the production of conjugated polyunsaturated fatty acids (especially the formation of oxidation products) indicates destruction of membrane fatty acids, this is not the only process which alters the fatty acid composition of membranes during ageing; a balanced dietary intake of omega-6 and omega-3 fatty acids must be taken into account [129].

BLOOD-BRAIN FATTY ACID TRANSPORT

By definition, essential polyunsaturated fatty acids must cross the blood-brain barrier, but the mechanisms of this transport are unknown. Several hypotheses have been proposed [130], including possible transport via the choroid plexus [131].

Age-related changes in the microcirculation include changes in the concentrations of trace elements, antioxidant enzymes (catalase is decreased, but not glutathione peroxidase) and fatty acids: the level of monounsaturated fatty acid increases, while the level of polyunsaturated fatty acids decreases and the level of saturated fatty acids remains stable [132].

The specific role of astrocytes in the synthesis of DHA from alpha-linolenic acid has not been fully elucidated [133, 134]. A possible co-operation between astrocytes and endothelial cells of micro-vessels has been proposed [135]. Depending on the conditions, serum free fatty acids or lipoprotein phospholipids could supply the brain with polyunsaturated fatty acids [136]. A particular phospholipid, phosphatidylcholine, may act as a fatty acid transporter to the brain [137].

The major problem in terms of nutritional physiology concerns determination of the bioavailability of alpha-linolenic acid and DHA [138].

Oleic acid does not cross the blood-brain barrier [139].

The factors that modify the blood-brain barrier are not known.

ANTIOXIDANTS AND UNSATURATED FATTY ACIDS IN THE BRAIN

A Medline database search reveals a small number of studies in this field: the combination of "polyunsaturated", "brain" and "ageing" provided only about one hundred references!

Although antioxidants are known to be important, particularly in the brain, the roles of the various components of vitamin E have been poorly elucidated. However, vitamin E deficiency is known to alter the fatty acid profile of the brain [140], and alpha-tocopherol is the only effective membrane antioxidant [141]. It is difficult to increase the quantity of vitamin E in the brain, which is unfortunate, as its 20:4ω6 and 22:6ω3 fatty acids are easily peroxidized [142]. The efficacy of protection against reactive oxygen species clearly decreases during ageing, accelerating destruction of membrane polyunsaturated fatty acids, which are less and less effectively renewed, constituting a vicious circle. An optimal dietary balance between omega-6 fatty acids and omega-3 fatty acids is therefore essential [143].

WHAT ABOUT SATURATED FATTY ACIDS?

The mechanisms of synthesis of saturated fatty acids have been documented for many years in the brain [144, 145] and in peripheral nerves [146]. Their intimate mechanisms are currently under investigation [147]. These mechanisms are now universally accepted, except that lignoceric acid (C24:0) can be partially derived from the diet [148, 149], as illustrated by the reduction of lignoceric acid accumulation in the brain by the presence of monounsaturated fatty acids in the diet in patients with adrenoleukodystrophy [150]. These studies have mainly concerned myelinization, rather than the ageing process. Polyunsaturated fatty acids could possibly be re-utilized to synthesize all types of fatty acids [151].

PRACTICAL APPLICATIONS

The polyunsaturated fatty acid requirement of the human brain is considerable during the neonatal period and remains high throughout life, in order to ensure turnover of cell membranes and to preserve the integrity of cell functions, otherwise the ageing process would be accelerated. However, these very long chains are not synthesized in the brain, or only in small amounts.

During the antenatal period, they cross the placenta in only small quantities and are not synthesized by the placenta. The brain synthesizes

only very small quantities in adults and almost none in the elderly [102]. It is therefore probably essential to provide them in the diet. However, baboon foetal tissue has been shown to synthesize DHA from alpha-linolenic acid [152]. Indeed, infant cerebellar grey and white matter acids is in relation to age and diet [153, 154].

For all ages in Human, proposed ratio omega-6/omega-3 by authorities is 5 to 6 [155], this number is also valuable for preterm infant formulas [156].

Cover of nutritional requirements in France: pregnant women and nursing mothers

During pregnancy, 600 grams of essential fatty acid are transferred from the mother to the foetus, which represents an enormous quantity of 2.2 grams per day, on average.

A study recently conducted in the Aquitaine region shows that women of childbearing age consume 90% of their linoleic acid requirement in their diet, but only 40% of their alpha-linolenic acid requirement [157]. Similar results have been found in other countries, such as Canada [158] and Sweden [159]. This deficiency could be prevented by the use of rapeseed, soybean or walnut oil. According to the recommended daily allowance during pregnancy (155], the dietary fat consumption by pregnant women must be globally increased by 15%, but with doubling of the consumption of DHA and cervonic acid. Fish with a real nutritional quality could be useful in this situation, but this may not be the case for fish derived from fish farms.

The increased requirements for various nutrients during pregnancy are not considerable, except for several minerals such as iron, zinc or certain vitamins, such as vitamin D, but they are important [160]. Following the example of supplementation of milk, It could be useful to add vitamin D to a seasoning oil, in view of its liposolubility.

However, the recommended daily allowances suppose that the future mother's diet is satisfactory, which is unfortunately not always the case, as illustrated by the SUVIMAX study. A significant proportion of women consume less than 2/3 of the recommended allowances for many vitamins, minerals and trace elements, including omega-3 fatty acids, as demonstrated by the Aquitaine study. The quality of the woman's diet obviously determines the quantities of omega-3 and omega-6 fatty acids received by the neonate [161]. However, the use of linseed oil in nursing mothers does not increase the DHA level of her milk [162]. In contrast, omega-3 long-chain fatty acid supplementation during pregnancy and breastfeeding increases the child's IQ [163, 164]. In an animal model, addition of long-

chain fatty acids combined with a reduction of precursors ensures a neuronal and glial profile similar to that obtained with maternal breastfeeding [165].

Blood lipid concentrations of docosahexaenoic and arachidonic acids at birth determine their relative postnatal changes in term infants fed breast milk or formula [166]. Moreover, alpha-linolenic acid in cholesterol esters is a marker of alpha-linolenic acid intake in newborns [167].

Better dietary polyunsaturated fatty acids for the brain

What is the better diet for the brain, a diet containing precursors (alpha-linolenic acid) or long-chain fatty acids (DHA, cervonic acid)? In other words, is it better to eat vegetables or fish, bearing in mind that eggs (so-called omega-3) are situated between the two in terms of omega-3, as they can contain both. In fact, alpha-linolenic acid and DHA are both necessary, but it would be preferable to consume the precursor that can be utilized by normal metabolism or oxidized when it is present in excess [168], rather than long-chain fatty acids, which are less effectively metabolized (toxic effects in the form of haemorrhages at very high doses, such as those consumed by Eskimos), as the brain is sensitive to excess levels [169, 20], although peroxidation is not increased provided vitamin E is present [170].

In view of current dietary habits, the most effective way to increase monounsaturated omega-9 and omega-3 fatty acids in the form of alpha-linolenic acid would be to eat rapeseed oil alone or mixed with other oils, provided they contain certain substantial quantities of rapeseed oil, which is not the case at the present time. The other oils rich in alpha-linolenic acid are soybean oil and walnut oil, but they have a much lower oleic acid content.

Fish and "omega-3" eggs provide substantial quantities of long-chain omega-3 fatty acids (EPA and DHA), but farmed fish must have been fed appropriate fats: the omega-3 content of their flesh can vary by a factor of 1 to 40 depending on whether they are fed vegetable oils (copra, etc.) or fish oils.

The nutritional quality of animal products can be improved by modifying the feed given to these animals. However, this measure is not very effective in ruminants, as the microbial activity of the rumen hydrolyses a considerable fraction of dietary polyunsaturated fatty acids, transforming them into non-essential fatty acids. However, this approach could be useful in monogastric species (such as pigs), substantial in poultry, spectacular for eggs, and essential in fish, especially carnivorous fish (75% of all fish).

Tables 1 and 2 show the multiplication factors obtained by providing

alpha-linolenic acid (in the form of rapeseed or linseed) or DHA (in the form of fish oil). The use of such products induces positive changes in consumers, especially on blood lipid parameters [171].

Table 1

Several examples of the multiplication factor obtained by feeding with alpha-linolenic acid (rapeseed or linseed).

	Alpha-linolenic acid	**Omega-3 long-chain fatty acids**
Pork rib-eye steak	3 to 6	0.9
Beef rib-eye steak	1 to 2	1
Chicken thigh	9	3
Egg	1 to 40	2 to 5

Table 2

Factor of multiplication by feeding with oils of fish

	Alpha-linolenic acid	**Omega-3 long-chain fatty acids**
Beef loin	1.3	1 to 2
Chicken thigh	1	2 to 7
Salmon	-	5 to 20
Egg	4 to 8	2 to 6

According to.(12, 172-181)

In fact, the most spectacular results presented in the above two tables are obtained by a very careful selection of the feed given to animals and would be relatively expensive. Fortunately, in practice, a team working in Brittany [171] has shown that replacement of part of the animal's feed by cooked linseed increases the cost of feed by about only 5% for beef cattle or poultry; which corresponds to an increase in the total cost of production of about 1 to 2%, for an extremely favourable result. It would be possible to exactly double the alpha-linolenic acid content of the meal, thereby reaching recommended daily allowances: for example, eggs would contain 12 times more of than this precious fatty acid, rabbit would contain 10 times more, chicken would contain 4 times more, and pork and milk would contain 3 times more!

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