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EFFECTS OF NUTRIENTS (IN FOOD) ON THE STRUCTURE AND FUNCTION OF THE NERVOUS SYSTEM: UPDATE ON DIETARY REQUIREMENTS FOR BRAIN. PART 2 : MACRONUTRIENTS

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Abstract: Among polyunsaturated omega-3 fatty acids, ALA (alpha-linolenic acid) provided the first coherent multidisciplinary experimental demonstration of the effect of diet (one of its major macronutrient) on the structure, the biochemistry, the physiology and thus the function of the brain. In fact, DHA (docosahexaenoic acid) is one for the major building structures of membrane phospholipids of brain and absolute necessary of neuronal function. It was first demonstrated that the differentiation and functioning of cultured brain cells requires not only ALA, but also the very long polyunsaturated omega-3 (DHA) and omega-6 carbon chains. Then, it was found that ALA acid deficiency alters the course of brain development, perturbs the composition of brain cell membranes, neurones, oligodendrocytes and astrocytes, as well as sub cellular particles such as myelin, nerve endings (synaptosomes) and mitochondria. These alterations induce physicochemical modifications in membranes, lead to biochemical and physiological perturbations, and results in neurosensory and behavioural upset. Consequently, the nature of polyunsaturated fatty acids (in particular omega-3, ALA and DHA) present in formula milks for infants (premature and term) conditions the visual, neurological and cerebral abilities, including intellectual. Dietary omega-3 fatty acids are involved in the prevention of some aspects of ischemic cardiovascular disease (including at the level of cerebral vascularization), and in some neuropsychiatric disorders, particularly depression, as well as in dementia, including Alzheimer's disease and vascular dementia. The implication of omega-3 fatty acids in major depression and bipolar disorder (manic-depressive illness) is under evaluation. Their dietary deficiency (and altered hepatic metabolism) can prevent the renewal of membranes and consequently accelerate cerebral ageing; nonetheless, the respective roles of the vascular component on one hand and the cerebral parenchyma itself on the other have not yet been clearly elucidated. Low fat diet may have adverse effects on mood. The nature of the amino acid composition of dietary proteins contributes to cerebral function; taking into account that tryptophan plays a special role. In fact, some indispensable amino acids present in dietary proteins participate to elaborate neurotransmitters (and neuromodulators). The regulation of glycaemia (thanks to the ingestion of food with a low glycaemic index ensuring a low insulin level) improves the quality and duration of intellectual performance, if only because at rest the brain consumes more than 50% of dietary carbohydrates, approximately 80% of which are used only for energy purpose. In infants, adults and aged, as well as in diabetes, poorer glycaemic control is associated with lower performances, for instance on tests of memory. At all ages, and more specifically in aged people, some cognitive functions appear sensitive to short term variations in glucose availability. The presence of dietary fibbers is associated with higher alertness ratings and ensures less perceived stress. Although an increasing number of genetic factors that may affect the risk of neurodegenerative disorders are being identified, number of findings show that dietary factors play major roles in determining whether the brain age successfully of experiences neurodegenerative disorders. Effects of micronutrients have been examined in the accompanying paper.

Abbreviations used. ALA: alpha-linolenic acid. EPA: eicosapentaenoic acid. DHA: docosahexaenoic acid. ARA: arachidonic acid. LA: linoleic acid.

Introduction

Some dietary deficiencies can alter cerebral function. Human physiology, and thus the brain, as any other organ, requires substances of dietary origin called nutrients, micronutrients and macronutrients including 8 essential amino acids; and 2 essential fatty acids, without which life would be impossible, they have been termed vitamin F: linoleic acid (LA) and alpha-linolenic acid (ALA). The brain thus needs nutrients to build and maintain its structure, both to function harmoniously and to avoid premature ageing. Indeed, the specialist functions of different cells requires nutrients to play particular roles, which implies specific needs for certain nutrients; the neurones and other brain cells do not escape this rule.

Recently published reviews in this journal discussed omega-3 fatty acids in psychiatry (mood, behavior, stress, depression, dementia and aging) (1), the other defined where to find omega-3 fatty acids and how feeding animals with diet enriched in omega-3 fatty acids to increase nutritional value of derived products for human (2). In continuation, the aim of this review is to summarise our knowledge concerning the effects of nutrients on the development and maintenance of the brain, and

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their implication in various processes, including the higher and neurosensory functions.

Cerebral development and omega-3 fatty acids. Experimental evidences

After adipose tissue, the human brain is the organ that contains the most fat. But cerebral fats play no part in storing or producing energy, they participate mainly in the architecture of the cell membranes, some being used for lipid signalling or for modulation of gene expression. All cells and organelles in the brain are very rich in polyunsaturated omega-3 fatty acids. In the nervous system, on average, one fatty acid out of three is polyunsaturated, thus obligatorily of dietary origin. A simultaneous deficiency of LA and ALA is not compatible with life. Such a deficiency seriously perturbs the fatty acid composition of all the organs, including the brain (3). Omega-3 fatty (ω3) acids are particularly concerned because on one hand the brain is extremely rich in these fats and on the other ALA is not consumed today in sufficient quantities.

On the glycerol backbone, position 2 of phospholipids is generally occupied by a polyunsaturated fatty acid, usually 20:4ω6 (ARA, arachidonic acid), 22:4ω6 (adrenic acid), 22:5ω3, and especially 22:6ω3 (DHA, docosahexaenoic acid, cervonic acid), and more rarely 20:5ω3 (eicosapentaenoic acid, EPA, timnodonic acid).

The first works to establish the relation between the effect of a macro-nutrient and the structure and function of the brain involved ALA. This acid is the first element of the omega-3 family, all the other acids of the family are derived from it. Initial studies showed that dissociated cultured brain cells needed, in order to differentiate and be functional, not only ALA, but also DHA and omega-6 acids (4). Then, in 1984, a study showed that a deficiency during perinatal period in ALA induced anomalies in the composition of different types of cells and organelles in the nervous system: neurones, astrocytes, oligodendrocytes, myelin, nerve endings, and endoplasmic reticulum (5), as well as mitochondria and endoplasmic reticulum. A very marked deficit in DHA is usually compensated for by excess 22:5ω6 (docosapentaenoic acid, DPA); however, this acid does not completely replace DHA in omega-3 deficient rats during early development (6). The total amount of polyunsaturated fatty acids is thus practically unaltered, as is that of saturated and monounsaturated fatty acids. It was then shown (7) in a same serie of animals each of which underwent biochemical, physicochemical, toxicological, electrophysiological, and behavioural tests, that dietary ALA can control certain neurosensory and higher functions such as learning; a quantitative decrease in these fatty acids in the brain results in impairment of membrane function (activity of enzymes, receptors, transporters). More precisely, analysis of the fatty acid composition of total phospholipids of the 11 brain regions in mice shows that the level of DHA is higher in the frontal cortex. Deficiency of ALA does not affect all structures to the same extent. Besides the hypophysis, the frontal cortex and striatum are most affected, with a decrease in DHA of about 40%. Omega-3 polyunsaturated fatty acids thus have a regional distribution in the brain and the effect of deficiency is "region-specific" (8, 9). Deficiency induces a decrease in DHA in the hippocampus associated with a decrease in the size of neurons but not in their number (10), with a specific decrease in omega-3 associated with a particular phospholipid, phosphatidylserine (11). In old rats, administration of fish oil increases the transcription of prealbumin in the hippocampus (12) and decreases nerve growth factor (13). Omega-3 fatty acids are potent neuroprotectors, associated with opening of background K+ channels (14); ALA also induces protection against ischemia in the spinal cord, thereby preventing both necrosis and apoptosis of motor neurons (15): this result strengthen the idea of an interesting potential therapeutical value of omega-3 fatty acids in neuronal protection. In relation with fatty acids profile changes, membrane fludity is altered (in nerve endings for example) of deficient animals, altering the effect of alcohol (16). At the nerve structure level, omega-3 fatty acids were preserved (with reuse of their very long chain derivatives, mainly DHA), since it was noted that a quantitative reduction of 21 in the diet resulted in a reduction of only 5 (at most) in the organs examined, and of only 2 in the neurones (5). There is a dose-effect relationship between the amount of dietary ALA and the level of DHA in the cerebral structures of both young (7) and adult animals (17). Dietary ALA is very probably elongated and desaturated in the liver into longer chains that are in fact the essential acids for the brain. If omega-3 fatty acids become deficient, preservation and reutilisation occurs. This is due to recycling induced by deacylation and reacylation decreasing by only 30 to 70%, whereas transfer between blood and brain decreases 40-fold (18). This explains the DHA deficiency of only 50%, first observed in neurones (5). Supplementation of female rats with ALA (60mg/kg) or DHA (6mg/kg) leads to the same omega-6/omega-3 long chain polyunsaturated fatty acids in mother tissues and in fetal and newborn brain (19). Interestingly, DHA body stores can be a significant source of brain DHA in animals that are fed ALA as the only source of omega-3 fatty acids (20). Formulas have been fed to baboon neonates (21).

In relation with alterations in fatty acid composition and membrane fluidity, ALA deficiency alters enzymatic activities, such as ATPase (7, 22), the effect of adding fish oil (rich in EPA and DHA) in the diet shows that various ATPase isoforms are not controlled the same way by ALA or by EPA or DHA (23). Electric field, membrane lipid composition and Na-K-ATPase molecular activity are linked, and DHA content of membranes determines molecular activity of the sodium pump (24). Moreover, up to 60% of the energy consumption in the adult brain is linked to Na-K-ATPase enzyme, and the brain uses at rest more than 50% of the dietary carbohydrates: this means approximately one fourth of the dietary energy is involved in only one enzyme activity in the brain. A deficit in

omega-3 fatty acids in rat could modify cerebral energy metabolism and perturb transport of glucose (25). In rat, deficiency of omega-3 fatty acids from conception adversely affects glucose tolerance assessed in adulthood (26). Dietary ALA deficiency induces a greater susceptibility of biological nervous membranes to stress.

DHA synthesis from ALA is probably extremely minute in brain, as desaturase activity is very low after birth in animal (27), but the question was raised on the DHA synthesis by some brain cells, mainly astrocytes (28). However, as any other cell, astrocytes in culture require DHA to restore the omega-6/omega-3 polyunsaturated fatty acid balance in their membranes phospholipids. In fact, astrocytes are mainly responsible for the polyunsaturated fatty acid enrichment in blood brain barrier endothelial cells in vitro (29). In contrast, foetal baboon is able to convert ALA to DHA (30). The question remains of the physiologic connections between animal and human, including cells model. Possible role of the choroid plexus in the supply of brain tissue with polyunsaturated fatty acids is speculated, as containing delta-6 desaturase activity (31).

In the rat, monoaminergic neurotransmission, especially in the frontal part of the brain, is specifically affected by deficiency of ALA (32). However, neither the density nor the function of dopamine transporters are affected (33). It is evident that there is a relation between the polyunsaturated fatty acids on one hand, and neurotransmission and behaviour on the other (32, 34). Supplementation with DHA and ARA in piglets prevents the decrease in dopaminergic and serotoninergic neurotransmitters in the frontal cortex caused by deficiency in ALA (35). There is a time lag between the incorporation of fatty acids in the brain and the improvement in learning performance (36). An intra-amniotic injection in animals deficient in DHA-rich triglycerides rapidly corrects a deficit in omega-3 fatty acids in the foetal brain.

Serotoninergic neurotranmission is affected by the deficiency in ALA, changing the synaptic level of 5-HT both in basal conditions and after pharmacological stimulation with fenfluramine (37). Cholinergic neurotransmission is also altered (38). Positron emission tomography (PET) in the conscious monkey showed that modulation of neuronal cholinergic transmission by DHA involves the cerebral blood flow as well as the cerebral structures (39). On the electrophysiological level, deficiency of ALA induces perturbations in the electroencephalogram (34). It also impairs the regulation and function of the pineal gland (hypophysis) at the level of the phospholipid molecular species, melatonin, and the products of lipogenesis (40). Dietary trans fatty acids act on endogenous neurotransmitter level during brain development, in piglets, and rat (41).

Nevertheless, consumption of omega-3 fatty acids exclusively is not sufficient to provide a normal fatty acid profile in nervous membranes. Very high dietary fish oil rich in EPA and DHA alters the brain polyunsaturated fatty acid composition (42). A diet rich in fish oil favours alertness and learning in young mice (43). Indeed, a balance between the essentials precursors in the circulating lipids if of vital importance for optimal deposition of DHA in the developing neural tissue. Moreover, only part of the dietary ALA is utilized for synthesis of brain DHA, the rest being in brain lipids synthesized de novo, thus metabolism of ALA extends well beyond the traditional desaturation-chain elongation pathway (44).

Behavioural changes (7) do not show up in all the tests (45), but more particularly in those relating to memorisation and habituation (46, 47). For example, 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. Defensive behaviour, anxiety, muscular function and neuro-muscular coordination were poorly affected by dietary ALA deprivation (48). These results have been confirmed many times using numerous models (49, 50).

The important question is whether deficiencies observed during the perinatal period result in anomalies that can subsequently be corrected, either simply over time or by supplying the fatty acids that were missing in the perinatal period; or are in fact the anomalies permanent? The rate of DHA recovery after dietary ALA deficiency is very slow (51, 52), including that of brain microvessels (53). After the deficiency is corrected, recovery of dopaminergic transmission (in the prefrontal cortex among others) is only partial (54). Even rats exposed from conception to a diet that produces a relatively modest decrease in brain DHA concentration exhibit alterations in adult behaviour indicative of altered dopaminergic function, some of these behavioural alterations are reversed by dietary remediation initiated at weaning (55). Thus, results obtained in animal models show that if rats made deficient in ALA acid are given a diet that is no longer deficient, then the brain (after a relatively long time) recovers its normal molecular composition, but remains less capable with regard to learning tasks. Only some of the adverse effects of DHA deficiency during neurodevelopment may be reversible with an omega-3 supplemented diet (56). Supplementations with phospholipids based on eggs or pig brain are more effective than triglycerides to restore the fatty acid composition to normal in brain (57) in all regions except the frontal cortex (9), as found for ARA (58); phospholipids from animal origin being more efficient than phospholipids from soybean (59). Generally speaking, soybean phospholipids may increase content in protein, polyunsaturated fatty acids and phospholipids in brain of mice, and improve learning and memory abilities in a dose-response manner (60). Supplementation with phospholipids containing long-chain omega-3 fatty acids (from egg yolks in this case) corrects the behavioural anomalies (9).

Brain development in the infant and omega-3 fatty acids

In the course of evolution, the dietary acquisition of DHA is thought to have greatly contributed to the development of the human brain (61). These fatty acids were obtained in fatty fish, seafoods, and eggs (62). At the end of gestation the foetus deposits each week about 70 mg of omega-6 acid in its brain (90% of it as ARA) and 30 mg of omega-3 acid (90% as DHA and 5% as EPA).

After birth, the newborn deposits each week about 66 mg of omega-6 fatty acids in his or her brain (90% in the form of ARA) and 30 mg of omega-3 fatty acids (90 % in the form of DHA and 5% in the form of EPA). Thus it is important for the mother to ingest sufficient polyunsaturated fatty acids, both precursors and the long chains. In fact, mother's milk is naturally rich in these substances. Brain from breastfed infants contains 1 g DHA, only 0.6 g in formula fed infants (63). The brains of newborns (who died of sudden infant death syndrome or accident) fed with formula milk contained less DHA than those who were breast-fed (64). The fatty acid reserves of a premature 35-week gestational age neonate represent less than one day of mother's milk, whereas infants born at term have several days reserves. In the case of premature babies, the benefits of supplementation with ARA and DHA are unquestionable (65). Expressed in kilos, an infant requires five times more lipids than an adult.

The nature of the omega-3 fatty acids (ALA or the longer carbon chains) present in formula milks exerts a fine control on various other biological activities such as quality of sleep and even some aspects of learning performance (66). Supplementation of formula milks with ALA has thus proved to be indispensable. Nevertheless, this is not sufficient to cover all the infant's needs for omega-3 poly-unsaturated fatty acids. In addition, the very-long-chain polyunsaturated fatty acids are consequently also required, notably DHA. Thus, though the interest and utility of dietary ALA is beyond doubt for the development and function of the human brain, on the other hand the role of the very-long-chain derivatives (especially DHA) are still under evaluation.

Several paediatric departments have now demonstrated that infants have better psychomotor development when given milk containing very-long-chain polyunsaturated fatty acids similar to those in mother's milk. For example, the developmental quotient of premature infants is proportional to the level of DHA in their red cell phospholipids (reflection of the situation in the brain). In premature infants followed-up for one year, 60% of the variation in the psychomotor development index and 82% of variation in the mental index could be explained statistically by the level of DHA in red-cell phospholipids (67). Neurological development is improved by dietary very-long-chain fatty acids (68). Very long chain polyunsaturated fatty acids have positive effects on motility measured at the age of 3 months (69). In fact, the status at birth is crucial: blood lipids concentrations of DHA and ARA at birth determine their relative postnatal changes in term infants fed breast milk or formula.

Results were similar when scored at one year (70). In England, the neurological status in children aged 9 years was better for those who had been breast-fed than for those who had received formula milk. Very-long-chain fatty acids (and notably those of the omega-3 family) were held to be responsible for this favourable result. More importantly, supplementation during pregnancy and lactation improves the IQ of children at the age of 4 years (71). Moreover, supplementation during childhood is associated with a decrease in blood pressure in the following years, which could contribute to decreasing cardiovascular risk in the adult (72).

Indeed, breast-fed infants archieve a higher rate or brain and whole body DHA accumulation than formula fed infants not consuming dietary DHA, thus dietary DHA should likely be provided during at least first 6 months of life (63). However, it should be remembered that, in the case of very-long-carbon-chain fatty acids, supplementation must provide simultaneously both omega-3 and omega-6, that is to say DHA and ARA. Results of randomized controlled trials shows that DHA and ARA supplementation (with indeed ALA) is efficient at the level of neurological, neuro-muscular and cognitive functions (73). In fact, in healthy women, conversion of ALA to longer chains polyunsaturates is quantitatively a minor route of utilisation (74), the rest being oxidized or in lipids synthesized de novo. The quantitative importance of the conversion of ALA to DHA in man is still unclear (75). It should be noted that egg extracts enriched in omega-3 and omega-6 have been used for several years in formula milks for infants, and that phospholipids from pig brain have been given to undernourished children (76).

Surplus DHA (in the rat) of dietary origin is stored in the adipose tissue (77), and this should be born in mind when preparing for pregnancy, because this store constitutes a reserve for the fœtus.

Evaluation of the effects of the incorporation of unsaturated dietary trans-fatty acids in the cerebral structures has already been performed in animals (78), it now remains to be carried out in humans. It should be taken into account that human milk contains trans mono- and polyunsaturated fatty acids (79).

Omega-3 fatty acids and neurosensory function

Vision is very relevant in the omega-3 fatty acid context since the retina is one of the tissues richest in polyunsaturated fatty acids of the omega-3 series. The retina preserves its DHA thanks to accelerated recycling either within the retina itself, or between the retina and the epithelium, or by selective uptake in the circulating blood (80). Experimentally, a deficiency in ALA modifies the distribution of membrane fatty acids in the retina, which perturbs the amplitude of waves a, and b of the electroretinogram (7), this has been confirmed in number of animal species an in human (81). Indeed, the nature of the

omega-3 fatty acids (ALA or the longer carbon chains) present in formula milks exerts a fine control on the visual performance of infants (66). Results of randomized controlled trials shows that DHA and ARA supplementation (with indeed ALA) is efficient at the level of visual functions (73). Dietary supplementation with phospholipids rich in DHA improves visual function of old control mice as well as those deficient in omega-3 polyunsaturated fatty acids (82). The effect of pure DHA (as ethyl ester) gives similar results (36).

In fact, DHA plays an important role in vision, involving the retina and brain but also photoreceptors, neurotransmission, activation of rhodopsin, development of cones and rods, neuronal connectivity, and maturation of cerebral structures. The effect of DHA deficiency on retinal function during development can be partly explained by modifications in retinal gene expression by direct or indirect mechanisms (83). During ageing of the retina, the number of phospholipids rich in DHA decreases (84). Perturbations in DHA metabolism are found in retinal degeneration (85). Retinis pigmentosa induces metabolic defect in chain elongation-desaturation mechanisms (86). Fish oil prevents ischemic-induced injury in the mammalian retina (87). Non physiological dietary trans fatty acids are found in retina (78) and long term of trans omega-3 polyunsaturated reduces the b-wave amplitude in rats (88). Since numerous behavioural tests in animals involve vision, it is important to verify that the learning deficits in mice deficient in ALA are not caused by alteration in vision (89).

Deficiency in omega-3 fatty acids perturbs hearing, particularly at the level of cerebral response. Moreover, it accelerates or advances the ageing of the auditory system: fatty acids can act at the level of the sensory receptors and the brain structures involved in hearing (90). In fact, the level of DHA in the maternal diet modulates the auditory system in rat litters (91). Phosphatidylcholine (lecithin) may be able to preserve the mitochondrial function of the cochlea, and thus protect against the loss of audition associated with ageing, maybe by playing a rate limiting role in the activation of enzymes protecting cell membranes from damage by reactive oxygen species (92). Results have also been found for olfaction: deterioration in tests on this form of perception is not due to a decrease in olfaction itself but to alteration of cerebral structures (93). A deficit in ALA impairs taste: for example, in the perception of a certain level of sugar flavour a larger amount of sugar is needed in ALA deficient animals (47).

Omega-3 fatty acids in psychiatric illness

This subject has been extensively treated in a recent review in this journal (1).

In what foods are omega-3 fatty acids present?

In many countries, including France, people, and specifically women, consume daily less than half the recommended dietary allowance (94, 95). The foods rich in omega-3 fatty acids are not very diversified in contrast to their prices (96, 97). The only foods that are effective dietary components (2), providing the tens of grams of ALA required daily, are the oils prepared from rapeseed, soybean and walnuts, plus a type of egg defined as for instance "Benefic" ® eggs (in France) or "Columbus eggs" ® (in US and most European countries) from laying hens fed linseed or eventually algae (quite apart from their other qualities, including "organic" or "special") and walnuts themselves.

The highly unsaturated long-carbon-chain omega-3 fatty acids (EPA and DHA) are presents in fish and the fatter the fish the richer in these acids. Mean dietary intake and food sources of DHA in French adult is about twice the French RDA; however, however extremely large variations are found (94). In contrast, in French Brittany, for people asked not to eat animal lipids, total amount of omega-3 long chain polyunsaturated fatty acids (EPA + DPA + DHA) was found much lower (95). Interestingly, the "omega-3" varieties ("Benefic" ® or "Columbus" ®) are nearly similar to natural eggs in terms of DHA content, and their consumption can favourably modify health parameters, for example it even reduces triglycerides response in mildly hypertriglyceridemic men and women and, for instance, increases serum levels of DHA in the mother and her child.

The effects of animal fodder on the nutritional value of derived products for humans differ greatly depending on the species (2, 96, 98). The consequences (qualitative and quantitative) of modifications in the composition of animal fodder on the nutritional value of derived products consumed by humans are greater in monogastric animals (pig and rabbit) than in polygastric animals (cows and sheep). This is because the hydrogenating intestinal bacteria of the latter transform a large part of the polyunsaturated fatty acids present in their fodder into saturated fatty acids, thus depriving them of their biological interest. Introducing linseed in all livestock diet increased improves favourably blood fatty acid composition of consumers of animal products (95).

It must be noted that usefulness of capsules as dietary complement is not clearly demonstrated, if not containing natural fish oil triglycerides (or phospholipids). In their natural state, omega-3 fatty acids are not isolated pure compounds, but are parts of large natural molecules, triglycerides and phospholipids, that are bioavailable by the human body. To obtain capsules containing enriched in either EPA or DHA, these compounds must be destroyed (hydrolysed) and the omega-3 fatty acids purified and generally stabilised as ethyl esters. This results in a product that is no longer natural, but a chemical. Indeed, a clear distinction must be made between dietary requirements and pharmacological doses, which are indeed much more important (2).

Fatty acids in neurological diseases and during ageing

The risk of Parkinson's disease has been reported to be correlated with the consumption of animal fats (99); milk products were first incriminated, then exonerated (100). Nutritional factors are difficult to determine, a French study showed a positive correlation with tea and a negative correlation with tobacco (101); another study showed caffeine to be a risk factor (102). Consumption of tomatoes has been reported to be favourable in an animal study (103), but this study found no correlation with carotenoids, antioxidants, or lycopene.

The interest of unsaturated fatty acids in the setting of prevention and follow-up of treatment in multiple sclerosis has long been debated. Dietary supplements may induce a decrease in the severity and frequency of relapses, at least over a period of 2 years (104), especially since a decrease in plasma and erythrocyte LA concentration has been reported (105). The specific interest of omega-3 fatty acids (106) could lie in the modulation of cytokines (107). The presence of anti-phospholipid antibodies in multiple sclerosis (108) is probably not related to dietary lipids.

In another domain, neurologically handicapped children absorb insufficient omega-3 fatty acids, as shown by the presence in their serum of 20:3ω9 and 22:5ω6 that are markers of deficiency, which is not favourable for the renewal of their already impaired cerebral structures (109). The alterations seen in certain diseases like infantile ceroid neuronal lipofuscinosis associated with dementia are secondary (110). The favourable effects of DHA in the setting of Zellweger syndrome (111) are only due to compensation of a defective metabolism.

Modifications observed during ageing both in animal models and in humans are complex and depend on whether the regions, structures, cells, organelles, or lipids are taken into account (97). Peroxisomal metabolism is implicated, in particular at the poly-unsaturated fatty acid level (112). Developmental maturation of hepatic omega-3 fatty acids metabolism can supply of DHA to brain and retina (113); however, interestingly, desaturase activity is dramatically reduced during aging (27). During late ageing in humans, excess nutritional LA is associated with a decline in cognitive performance, whereas the opposite is true for fish oils. An age-related increase in reactive oxygen species production is linked with decrease in polyunsaturated fatty acids (mainly omega-3 fatty acids) and a diet enriched in EPA has anti-oxydant properties which may play a key role in reversal of some age-related deficits (114). Indeed, the decreased level of polyunsaturated fatty acids in the aging brain may result from poor transfer through the blood-brain-barrier, or from a decreased rate of incorporation into membranes, or a decrease in the activities of delta-6 or delta-9 desaturase enzymes; added oxidative stress leading to an increase of free radicals leading to decrease in membrane fluidity (115). Phosphatidylcholine improves memory, learning, concentration, memorisation of words, and mood in elderly subjects with cognitive decline (116). Vitamin B12 associated with phosphatidylcholine improves learning performance, at least in ageing mice (117). Interestingly, oral choline increases choline metabolites in human brain (118). It is certain that an adequate intake of omega-3 fatty acids ensures the renewal of nervous membranes and thus protects, to a certain extent, against cerebral ageing. During aging in animal model, dietary ALA deficiency alters learning ability but not selective attention (119). Supplementation uniquely with omega-3 fatty acids induces behavioural manifestations that are not the same in both young and old animals: it favours alertness and learning in young mice, but, on the other hand, it decreases motor activity and learning in old mice (43). A balance diet in omega-3 and omega-6 fatty acids must be used.

As far as multiple neurological and psychiatric diseases are concerned, in the specific setting of membrane physiology, numerous research teams are studying (on both animal and human models) anomalies in the metabolism of phospholipids. This is being carried out both in the brain and other tissues and regulation at the level of lipid messengers. However, since alimentation is not directly concerned, this subject is not dealt with in this review.

Various effects of omega-3 fatty acids

Polyunsaturated fatty acids, specially omega-3 fatty acids, function mainly by altering membrane lipid composition, cellular metabolism, signal transduction and even regulation of gene expression, this latter aspect being currently actively experimented (120). Genetic apparatus of neurons (and probably other brain cells) respond sensitively to the fatty acid taken up with the food, especially omega-3 fatty acids. The observation that ALA and EPA+DHA affect expression levels of number of genes in brain, such as synaptic plasticity, cytoskeleton and membrane association, signal transduction, ion channel formation, energy metabolism and regulatory proteins (121, 122) opens the way to the question whether these fatty acids affect brain genome in free form or through their effect on composition and biophysical properties of neuronal membranes. In this respect, it is interesting to note that dietary ALA induces (in the liver) changes not only in fatty acid composition of the nuclear membrane lipids, but also in the specific activity of NTPase involved in nuclear function (123). Altered lipid composition of nuclear membranes may affect permeability properties, allowing transfer of compounds (such as messengers), which may change gene expression or suppression. Thus, alteration in membranes architecture and function coupled with alterations in gene expression profile may contribute to the beneficial impact of omega-3 fatty acids on cognitive functions. Indeed, cognitive processes are very complex and cannot be traced back to a simple accumulation of DHA in neuronal membranes; although brain tissue has an absolute requirement for its function, at least by ensuring proper biophysical property and structural integrity of all

neuronal membranes, including nerve endings. Interestingly, the membrane deterioration theory is considered one of the most important in explaining the aging phenomena. Low fat diet may have adverse effects on mood (124).

Mounsaturated, saturated fatty acids and cholesterol

In brain the omega-9 fatty acids are represented by oleic acid (18:1 omega-9) as well as by very considerable amounts of longer carbon-chain derivatives, mainly nervonic acid (24:1) especially in myelin. For many organs, including peripheral nervous system, endogenous synthesis does not compensate for the absence of oleic acid in food, which must therefore be provided in the diet (125). This fatty acid is thus partially essential, especially during pregnancy and nursing, at least in the rat. The absence of changes in the concentration of oleic acid in brain structures despite changes in the oleic acid level in the diet suggests several hypotheses. Either the nervous system has priority in the capture of oleic acid, or specific transport systems exist at the blood-brain barrier, or the brain can synthesise all the oleic acid it needs, independently of its presence in the diet (126). In fact the brain does possess an active stearyl desaturase (127). Interestingly, in mice with accelerated senescence, a decrease in delta-9-desaturase is observed in the hippocampus, which could be linked with behavioural disturbances (128).

The mechanisms involved in synthesis of saturated fatty acids in the brain have been known for many years (129, 130); their precise mechanisms are currently being studied, especially the question whether lignoceric acid (C24: 0) can be partly of dietary origin (131, 132), as suggested by the decreased lignoceric accumulation in the brain due to monounsaturated fatty acids in the diet of patients with adrenoleukodystrophy (133). At the present time, interest in understanding the metabolism of saturated and monounsaturated fatty acids has its clinical application in the attempts to treat adrenoleukodystrophy using oils rich in monounsaturated fatty acids (known as Lorenzo's oil) which, by competition, decrease the uptake of saturated fatty acids by the brain, thus reducing their toxic accumulation.

It cannot be excluded that polyunsaturated fatty acids are reused to synthesise fatty acids of all kinds, including saturated ones; especially since a not inconsiderable part of dietary polyunsaturated fatty acids is oxidised, especially during pregnancy.

Ever since the introduction of statins for the treatment of hypercholesterolaemia, the dogma of the total synthesis of cerebral cholesterol by the brain parenchyma has been challenged. Especially now that a negative relationship has been suggested between the risk of Alzheimer's disease and the level of cholesterol synthesis by the neurones. This is because the passage of statins across the blood-brain barrier induces a reduction in cholesterol synthesis, leading to a decrease in Abeta-amyloid peptides (134). Although early studies demonstrated the loss of cholesterol and other lipids in the demented brain, these findings have been poorly connected with Alzheimer disease pathogenesis; in contrast, the finding that cholesterol can modulate the concentration of potentially toxic Abeta has promoted research on cholesterol reducing drugs, now evaluated for treatment of Alzheimer disease (135). Growing evidence indicate that changes in brain cholesterol and variations in neuronal membranes structures are involved in the development of Alzheimer disease (136). In fact, during cerebral development, at least in cultured rodent cells, it seems that cholesterol synthesis by neurones decreases, and that the rodent cells import cholesterol from astrocytes via the lipoproteins. In good agreement, the neurones use cholesterol from glial cells to elaborate their synapses (137).

Proteins and dietary amino acids

Indeed, brain enzymes, proteins, and peptides consist of amino acids, some being derived from dietary proteins. The agents responsible for transmission between neurones are substances eventually formed of essential amino acids supplied by dietary proteins. The effects of the absence of certain foods on the brain also proves their essentiality. Some genetic deficiencies cause alterations in the brain, simply because certain nutrients are not metabolised normally, as in phenylketonuria, caused by abnormal metabolism of an essential fatty acid, tryptophan.

The brain needs a continual supply of amino acids for synthesis certain neurotransmitters, notably the catecholamines and serotonin. Moreover, it has been speculated that human intelligence has its roots in the growth of dopaminergic systems in the development of human cognition (138). The macronutrients participate in the formation of neurotransmitters, in particular during development (139). The regulation of protein syntheses by the level of dietary carbohydrates is no longer in doubt (140). The quality of dietary proteins influences the nature and the quantities of cerebral proteins and neurotransmitters. Thus, the amino acid profile of the cerebral extracellular milieu is a function of the content and nature of dietary proteins (141).

Malnutrition (an extreme case is kwashiorkor) implies protein deficiency and can severely alter the elaboration and functioning of the brain, as many epidemiological studies have demonstrated (142). Not only young children but also adolescents are affected (143). Two brain structures seem to be particularly vulnerable, the hippocampus and the hypothalamus (144); moreover, visual and auditory evoked potentials are altered (145). The nutritional quality of proteins is extremely important: the presence of indispensable amino acids (in quantity and proportion) determines their biological value. Overall, proteins of animal origin are of greater value than those of vegetable origin. Thus, over consumption of tofu (bean curds), that is to say soy bean vegetable proteins, has been implicated in more rapid changes in cognitive tests during

ageing (146). In practice, as the human body does not possess a reserve of proteins, they need to be eaten at every meal, especially breakfast. Milk and milk products are especially useful in this respect.

In any case, the effect of essential amino acids on brain functioning (including mood, sleep, eating) is a field of fundamental and clinical research that is booming. Dietary tryptophan, precursor of serotonin, plays a specific role (147). Apart from modulating appetite and satiety, it is involved in numerous functions such as sleep, sensitivity to pain, regulation of blood pressure, and the control of mood (148). Serotonin cannot cross the blood-brain barrier (BBB), therefore it plays no role in cerebral nutrition. On the other hand, tryptophan is of interest because it can cross from the blood into the brain thanks to specific transporters. The efficacy of its action is illustrated by the following observation: tryptophan hydroxylase, the rate-limiting enzyme of serotonin synthesis (5-HT), is not saturated under normal physiological conditions; consequently, each increase or decrease in the concentration of tryptophan in the brain induces an increase or a decrease in serotonin synthesis (149). A common mechanism of action with tryptophan would implicate serotonin in food intake on one hand and in depression on the other (150). Dietary tryptophan thus has an effect on mood and also on depression (151). The kind of food in the diet controls the level of tryptophan in the blood, and thus modulates food intake (152). The satiating effect of different proteins (beef, chicken, and fish) is related to a certain extent to their tryptophan content (153). The satiating effect of nutrients varies, the proteins having a stronger effect than lipids or proteins. In fact, changes in serotonin concentration modulate dietary behaviour (154). This neurotransmitter plays a role in the processes determining hunger during consumption of food and in the sensation of satiety that follows (155). A marked deficit can worsen cognitive dysfunction in schizophrenics, but without inducing mood swings or abnormal movements (156). Protein, amino acids and the control for food intake (157) is out of the scope of this review.

Transport of tryptophan across the blood-brain barrier decreases during ageing (158). Due to its competition with tryptophan for passage into the brain, it is not surprising that tyrosine can improve cognitive performance and appetite, in particular during anorexia due to exercise; however, these are very preliminary results obtained in animals (159).

Certain amino acids are transported by specific routes. Thus glutamine is exported by astrocytes to neurones to satisfy their need for a neurotransmitter, glutamate (160). Carnitine is probably conveyed through the BBB by a transporter (161), and cultured cerebral capillaries have shown that it is probably a specific transporter (162). The same is true for taurine, both in culture (163) and in vivo (164). Glutathione is also able to cross the BBB (165).

Brain interstitial fluid contains numerous peptides at higher concentrations than in blood plasma. They must therefore have been transported, unless they are the result of de novo brain synthesis, as already described for beta endorphin, growth hormone-releasing factor (GHRF), and calcitonin. And this is possible because proteins can be transferred across the BBB (166).

Brain and glucose

The brain requires a steady supply of energy permanently day and night: (one hundred mg per minute of glucose) and an oxidising agent (oxygen). At rest, the adult brain uses about 20% of the dietary energy consumed and 20% of the oxygen inhaled. In adults, the brain represents no more than 2% of bodyweight. In children, consumption is even higher and reaches 60% in newborns. A child's brain consumes twice as much glucose per unit of weight as that of an adult (167, 168), which explains the undesirable results of hypoglycaemia (due to a poorly nutritional breakfast) on performance at school. It is thus logical that cerebral function, and thus the equilibrium and efficacy of intelligence depends on the quality (and quantity) of dietary energy. During sleep, the brain continues to consume glucose; but during a nightmare total brain consumption increases by 16%, whereas the increase is 30% in the frontal cortex (169). This consumption can be recorded by the positron camera.

Glucose produces 18 times more energy in the presence of oxygen than in its absence; brain fuel is only efficient in the presence of an oxidant. The hypoglycaemia can only be avoided thanks to carbohydrates (starchy foods), that is to say whose glycaemic and insulin indexes are low, and whose distribution in the organism is thus slow, but regular and effective, which ensures maximum efficiency of the brain.

Since the brain runs only on glucose, and has no reserves (except for a very small amount of glycogen), satisfaction of its needs depends on supply, and thus depends on diet, as carbohydrate reserves in the human body are very limited. Not all the regions of the nervous system are equally sensitive to a shortage of glucose: those that are phylogenetically the oldest and anatomically the deepest are the most resistant. On the other hand, the frontal cortex is the organ most susceptible to hypoglycaemia. Thus the cognitive performance of volunteers is related to the level of glucose in the blood (170). After hypoglycaemia, recuperation of cognitive performance does not immediately follow recovery of the blood glucose concentration and the resolution of symptoms (171). In the rat, cognitive activity decreases the amount of glucose present in the extracellular medium of the hippocampus; administration of glucose reverses the decrease and improves cognitive performance (172). Apart from the simple provision of energy, glucose also affects memorisation by acting on the cholinergic system (173). Interestingly, glucose transporter type 1 deficiency syndrome is a treatable epileptic encephalopathy resulting form impaired glucose transport into the brain (174). Substances such as phenobarbitone and caffeine should be

avoided, as they inhibit glucose transport (175).

Thus, intellectual efficiency during the morning is determined by the quality of the first meal of the day (176). Breakfasts that result in a good glucose level at the end of the morning also ensure that the student is in a good mood and intellectually more efficient during the morning. In order for cognitive performance to be effective, the energy expenditure must also be taken into account (177).

In young adults, poor regulation of blood glucose leads to poor memorisation, and this is reversed after ingestion of glucose (178); glucose (but not saccharine) improves face recognition (179). In fact, the most absorbing tasks, those that require most attention over a long period, are those that benefit most from good glucoregulation. Thus, it has been shown that glucose influences performance of car driving in a simulator, but only for distances greater than 70 kms (180).

Recently, it has been clearly demonstrated the people whose glucose level is poorly regulated have a reduced intellectual capacity, in particularly the elderly (mean decrease of at least 8 to 10%). Briefly, the response to difficult or complex tasks is better the more the glucose level is favourable. Giving the elderly carbohydrates improves their mental performance, whereas sweeteners such as aspartame or saccharine have no effect, proof that it is indeed glucose that is responsible (178). Cognitive performance is associated with glucose regulation in elderly subjects (181), and this can be demonstrated by electroencephalography (182). In volunteers aged about 55 years, increased blood insulin concentration is related to a decrease in cognitive function and the risk of dementia in women. This implies that excess insulin can be directly toxic to the brain, rather than just increasing cardiovascular risk (183). In any case, persistent impairment in glucose tolerance in elderly subjects is associated with a moderate decrease in cognitive performance; raised insulin levels could participate in this association (184).

In the case of diabetics who suffer, by definition, from poor glucoregulation, tests show that memory is perturbed, mathematical calculations are slightly affected, and psychomotor efficiency diminished. Diabetes type II, non-insulin-dependent diabetes, increases the risk of cognitive dysfunction (185, 186). Unfortunately, obesity is present in diabetes in approximately 70% of cases. Generally speaking, the poorer the glucoregulation, the less good are the cognitive tests (and memory) (181). Thus, the intellectual performance of elderly people with type II diabetes is less good than that of a normal population of the same age; in non-diabetics, the best results are obtained by those with the best glucoregulation (178, 184). These findings have not yet been explained; they are not of course catastrophic, but they are worrying.

In animals with experimental diabetes, ginkgo extracts compensate for the learning, memory, and cognitive deficits, and restore cerebral energy metabolism to almost normal levels (187), in particular by ensuring better energy metabolism at the mitochondrial level (188). In human diabetics, raised levels of blood triglycerides contribute to lowering the ability to perform tasks based on short-term memory (189). Gestational diabetes (or its early signs) in mothers disturbs the attention level and motor function in their children, but not their cognitive performance. This disturbance is proportional to the degree of glycaemic control in the mothers (190).

The interaction of carbohydrates with other constituents of meals is still largely unknown. It cannot be excluded that numerous substances that increase cognitive performance may act at the glucose level, either by increasing glucose availability or its uptake by the brain (191). In fact, eating breakfast improves cognition via several mechanisms, one of which is the increase in blood glucose (192). In volunteer students, cognitive performance after a meal is improved by consumption of fats, and concomitantly glucose metabolism is stabilised. Ingestion of carbohydrates improves short-term memory and induces greater precision in performance of tasks, while proteins improve attention (193). In general, each macronutrient has a specific action on cognition: proteins, carbohydrates, and lipids improve memory performance in the normal adult, independently of the increase in blood glucose (194).

A interesting concept: glycaemic index

Sugar must arrive slowly but regularly in the blood in order to furnish an extremely regular supply for the brain; this is achieved mainly thanks to a gastric emptying time that is as long as possible, the nature and composition of meals that provide the carbohydrates, and of digestion and intestinal transit times that are as slow as possible. This results in a low glycaemic index (and low insulin secretion), which is the desired objective, because this index is the most reliable measurement that current scientific and medical knowledge can provide. The insulin index is certainly more precise (195), but it is more difficult and more expensive to perform.

All foodstuffs containing carbohydrates do not induce the same glucose response in the organism (for different foods, glucose passes more or less rapidly and massively into the blood); hence the need for a glycaemic index for foods. This is based, for an equal amount of carbohydrate, on the hyperglycaemic effect (raised level of glucose in the blood) of a given food compared to a solution of glucose. A glycaemic index has been established to classify foods according to the extent and duration of the rise in glucose level that they induce when ingested, compared to that obtained by an equivalent amount of glucose.

In fact, detailed examination of the results shows that the kind of carbohydrate (simple or complex) does not permit the glycaemic index to be inferred. Thus the index of glucose being 100 %, that of fructose is only 23 %, which explains why fruit have such low indexes. The disaccharides (consisting by definition of two simple sugars) have moderate indexes, from 73 % for honey (because it contains a good amount of glucose)

to 65% for sucrose (found in lump sugar and sweet drinks), and the index descends to 46 % with lactose from milk.

The presence of fats (eaten at the same time as carbohydrates) decreases the glycaemic index: whereas it is 65 % for sucrose, it falls to 49 % for chocolate (consisting of fats and sugars). The combination of fats and proteins lowers the index further: to 45 % for pasta, 39 % for ravioli (due to the presence of proteins), and 32 % for egg pasta (proteins + fat). Similarly, the skimmed milk index [32%] is lower than that of lactose [46%] because of the presence of proteins, and that of whole milk is even lower [27%] due to the presence of both proteins and fats. For bread, the glycaemic index is very variable depending on the bread chosen: it is relatively low for the French traditional baguette [57%], low for bread made with bran flour (the fibres lower the index). Moreover, in general bread is practically never eaten alone: in its role as cereal it is present at all meals, but is normally accompanied by other foods.

In practice, there can be cooperation between nutrients present in the same foodstuff: some simple sugars like those in prunes behave like "slow" sugars due to the presence of fructose and sorbitol, and this cooperation is amplified by the action of poly-phenols and fibres. Other factors can also intervene, the granulometry (whole or mashed potatoes), the method of cooking, and time of day.

In any case, satiety is inversely proportional to the glycaemic index of the food. That is to say, the "slower" the food the greater its ability to satisfy hunger. Interestingly, in the obese adolescent, snacking after a meal with a high glycaemic index is 81% greater than after a similar meal but with a low glycaemic index (196).

Conclusions

Some other food constituents are of interest. For instance, the brain consists mainly of water, either intracellular or extracellular (consisting not only of the liquid that surrounds the cells but also the cephalo-rachidian liquid, which represent 12 to 19% of brain volume). This organ is very sensitive both to a deficit in water and to an excess (the redoubtable oedema). However, practically nothing is known concerning the mechanisms involved in maintaining the level of water in the brain (197). The integrity of the blood-brain barrier (that is beyond the scope of this review) is ensured by a correct supply of nutrients to the brain. The primary site of action is situated at the level of the endothelial cells of the cerebral microvessels.

Some other topics are not examined in this review: interestingly, adequate nutrition in patients with head injury reduces length of the rehabilitation in patients with head injury in both the acute ward an in rehabilitation unit (198).

This work is the sequel to more general works that have been published on the subject, initially to define it (199), and then to deal with practical problems (96).In conclusion, Brain diseases, especially during aging, can be due to dietary deficiencies. Alterations of mental and behavioural functions that can be corrected by dietary measures involving macronutrients (as well as in micronutrients, see the accompanying paper), but only to certain extend.

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