

EFFECTS OF NUTRIENTS (IN FOOD) ON THE STRUCTURE AND FUNCTION OF THE NERVOUS SYSTEM: UPDATE ON DIETARY REQUIREMENTS FOR BRAIN. PART 1: MICRONUTRIENTS

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Abstract: The objective of this update is to give an overview of the effects of dietary nutrients on the structure and certain functions of the brain. As any other organ, the brain is elaborated from substances present in the diet (sometimes exclusively, for vitamins, minerals, essential amino-acids and essential fatty acids, including omega-3 polyunsaturated fatty acids). However, for long it was not fully accepted that food can have an influence on brain structure, and thus on its function, including cognitive and intellectual. In fact, most micronutrients (vitamins and trace-elements) have been directly evaluated in the setting of cerebral functioning. For instance, to produce energy, the use of glucose by nervous tissue implies the presence of vitamin B1; this vitamin modulates cognitive performance, especially in the elderly. Vitamin B9 preserves brain during its development and memory during ageing. Vitamin B6 is likely to benefit in treating premenstrual depression. Vitamins B6 and B12, among others, are directly involved in the synthesis of some neurotransmitters. Vitamin B12 delays the onset of signs of dementia (and blood abnormalities), provided it is administered in a precise clinical timing window, before the onset of the first symptoms. Supplementation with cobalamin improves cerebral and cognitive functions in the elderly; it frequently improves the functioning of factors related to the frontal lobe, as well as the language function of those with cognitive disorders. Adolescents who have a borderline level of vitamin B12 develop signs of cognitive changes. In the brain, the nerve endings contain the highest concentrations of vitamin C in the human body (after the suprarenal glands). Vitamin D (or certain of its analogues) could be of interest in the prevention of various aspects of neurodegenerative or neuroimmune diseases. Among the various vitamin E components (tocopherols and tocotrienols), only alpha-tocopherol is actively uptaken by the brain and is directly involved in nervous membranes protection. Even vitamin K has been involved in nervous tissue biochemistry. Iron is necessary to ensure oxygenation and to produce energy in the cerebral parenchyma (via cytochrome oxidase), and for the synthesis of neurotransmitters and myelin; iron deficiency is found in children with attention-deficit/hyperactivity disorder. Iron concentrations in the umbilical artery are critical during the development of the foetus, and in relation with the IQ in the child; infantile anaemia with its associated iron deficiency is linked to perturbation of the development of cognitive functions. Iron deficiency anaemia is common, particularly in women, and is associated, for instance, with apathy, depression and rapid fatigue when exercising. Lithium importance, at least in psychiatry, is known for a long time. Magnesium plays important roles in all the major metabolisms: in oxidation-reduction and in ionic regulation, among others. Zinc participates among others in the perception of taste. An unbalanced copper metabolism homeostasis (due to dietary deficiency) could be linked to Alzheimer disease. The iodine provided by the thyroid hormone ensures the energy metabolism of the cerebral cells; the dietary reduction of iodine during pregnancy induces severe cerebral dysfunction, actually leading to cretinism. Among many mechanisms, manganese, copper, and zinc participate in enzymatic mechanisms that protect against free radicals, toxic derivatives of oxygen. More specifically, the full genetic potential of the child for physical growth and mental development may be compromised due to deficiency (even subclinical) of micronutrients. Children and adolescents with poor nutritional status are exposed to alterations of mental and behavioural functions that can be corrected by dietary measures, but only to certain extent. Indeed, nutrient composition and meal pattern can exert either immediate or long-term effects, beneficial or adverse. Brain diseases during aging can also be due to failure for protective mechanism, due to dietary deficiencies, for instance in anti-oxidants and nutrients (trace elements, vitamins, non essential micronutrients such as polyphenols) related with protection against free radicals. Macronutrients are presented in the accompanying paper.

Introduction

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. In consequence, some dietary deficiencies can alter cerebral function. Human physiology, and thus the brain,

requires substances of dietary origin called nutrients: vitamins, macroelements such as carbon, oxygen, hydrogen, calcium, and magnesium; trace elements such as iron, magnesium, selenium, iodine; as well as copper, zinc, manganese, 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); DHA being conditionally

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essential. The brain thus needs nutrients to build and maintain its structure, both to function harmoniously and to avoid premature ageing.

Certainly the brain has priority in supplies, and it is served before the other organs. If needs be, it can even draw on their reserves and weaken them. Of course, the brain is extremely well protected by a "wall", the blood-brain barrier. But that does not alter the fact that it still needs food and nutrition, and that it is best not to ingest toxic substances.

This work is the sequel to more general works that have been published on the subject, initially to define it (1), then to deal with practical problems (2). It is evidently impossible to carry out experiments on samples taken from the living human brain to determine the effects of nutrients on brain chemical composition and biochemical mechanisms. Thus most results are obtained using animal experiments and then confirmed clinically.

Vitamins

All the vitamins are indispensable for normal functioning of the brain. However, some of them are very closely involved in the functioning of neurones and other brain cells. In fact, it is even possible to assign a specific efficacy to each vitamin for certain activities in the cognitive domain. Thus, thiamine (B1), riboflavin (B2), niacin (B3), and the folates improve the level of abstract thought and lead to a more favourable biochemical status; vitamin C improves visuo-spatial performance; vitamins B12, B6, A, and E ensure a better visuo-spatial memory and improve abstraction test results (3). It has even been calculated that during ageing, intellectual levels are best protected with daily vitamin intakes equal to or higher than 150 mg for vitamin C (French Recommended dietary allowances, RDA, 110), 3 mg for vitamin B6 (RDA, 5), and 3 mg for riboflavin (RDA, 1.6) (4). As far as pregnant women and infants are concerned, the major purveyors of mental deficiency in the world are protein-energy malnutrition and deficiencies of iron and iodine. However, deficiencies of vitamin A and zinc have also been incriminated (5).

During ageing the antioxidants protect against peroxidation (and other damage) and are thus involved in the prevention of progressive deterioration of memory (6). Consumption of fruit, vegetables, and vitamin E do not totally explain all the favourable effects on cognitive performance (7); that is why other antioxidants are being considered, among them the polyphenols. Numerous other vegetable substances could be advantageous (8). Especially since extracts of *Ginkgo biloba* are interesting (9, 10).

Vitamin A

In the nervous system, vitamin A is primordial at many levels: for example in the synthesis of visual pigments (the eye is part of the nervous system), the control of differentiation and proliferation of cells during foetal life. It has an important role

in the neutralisation of the toxicity of certain substances by the liver, i.e. hepatic detoxification, thus indirectly protecting the brain. Retinol, and especially its active form, "all trans" retinoic acid, carry on their molecular actions in the different target cells by binding with certain receptors of cell nuclei. Vitamin A and the retinoids are even implicated in synaptic plasticity in a brain region, the hippocampus, suggesting they have a role in the establishment and maintenance of cognitive functions (11). Vitamin A can act as a "gene regulator" and as a nuclear receptor modulator; as shown, for instance in the striatum, a region highly sensitive to vitamin A bioavailability; in relation with neurobiological alterations and spatial learning impairments observed in vitamin A-deprived animals (12).

Vitamin A, and more particularly its precursor, beta-carotene, contribute to the stabilisation of biological membranes. Vitamin A and the carotenoids (among them beta-carotene, provitamin A) participate with other micronutrients (notably vitamins E, C, and selenium) in the protection of tissues, in particular nervous tissues, from aggression by free radicals or active forms of oxygen. Food of animal origin supplies ready-to-use vitamin A, whereas that of vegetable origin contains a precursor that has to be transformed in the body. Vitamin A of animal origin is thus six times more efficacious than vegetable provitamin A. Due to this, vegetarians can be deficient in vitamin A if they do not eat sufficient fruit and coloured vegetables. Retinol-rich products are liver, milk, butter, eggs, some cheeses, and fish; while green vegetables, carrots, coloured tubers, yellow fruit, and oranges are rich sources of carotenoids. The addition of vegetable oil increases by at least six fold the bioavailability of beta-carotene in the intestine.

Vitamin B1, thiamine

This vitamin is extremely important for the brain, because it facilitates the use of glucose, thus ensuring the production of energy. Deficiency results in a very severe disease, beri-beri. After six days of vitamin B1 deficiency in young volunteer men, are observed signs of lassitude, lower intelligence, irritability, and cramps, and electrocardiographic abnormalities. If the deficiency continues, the patient complains of pain, particularly of the extremities that is often painful. All these signs disappear when the vitamin is readministered. Indeed, thiamine utilisation is found in alcohol abusers (13). A borderline thiamine status in women is associated with mood swings (14); in any case, it is certain that this vitamin modulates cognitive performance (15), especially in the elderly (16). Reduced thiamin (as well as reduced vitamin C, cobalamin, homocystein and alpha-tocopherol) can contribute to the development of Alzheimer disease (17). In rat, thiamine deficiency results in selective neuronal cell death in thalamic structures; this may be related with increased brain endothelial nitric oxide synthase expression (18).

Vitamin B3 (PP or niacin) and B6 (pyridoxin)

A deficiency in this vitamin cause Pelagra, it is eventually associated to alcoholism (19). Between depression due to vitamin B1 deficiency and the excitation induced by deficiency of B3, the appropriate balance can be found thanks to vitamin B2 (riboflavin), which ensures the harmonious use of the other two vitamins. The greatest alimentary catastrophes the world has ever known affected two continents and were due to vitamin deficiency: beri-beri in Asia caused by the consumption of polished rice and pellagra in North America due to incorrectly cooked maize. The concentration of vitamin B6 (pyridoxin) in the brain is one hundred times greater than in blood. In general, by ensuring synthesis of chemical mediators, vitamin B6 combats asthenia, irritability, and depression; vitamin B6 is likely to benefit in treating premenstrual symptoms and premenstrual depression (20). The highest levels of B6 in the blood are associated with the best performance in memorisation tests (21). Pyridoxin could play a role in tryptophan metabolism, increasing the production of 5-hydroxytryptophan (22).

Vitamin B9 (folic acid)

During pregnancy, deficiency in vitamin B9 induces major anomalies during the elaboration of the nervous system in the infant, but this can be reduced by 85% with systematic folate supplementation (23), few weeks before starting pregnancy. In the elderly, deficiency decreases intellectual capacity (24, 25) and impairs memory (26). Foods rich in folate are liver, eggs, many green vegetables (cress, spinach, leeks, lentils, asparagus, broccoli, cauliflower), and maize, chickpeas, almonds, chestnuts (2).

Vitamin B12 (cobalamin)

Deficiency in vitamin B12 in humans and in animal models induces neurological disorders, psychic disturbances, and haematological alterations. In fact, the neurological signs can largely precede the haematological signs. Malaise is extremely frequent. Early diagnosis is essential to avoid irreversible damage to the nervous system. The main symptoms are memory loss, pain, and abnormal sensations at limb extremities. Vitamin B12 deficiency during childhood not only retards myelinisation (27) but causes damage, in particular neurological, that persists (28). It can also cause nerve injury leading to blindness (29). It is obvious that vegans (excluding all food form animal origin) and even ovo-lacto-vegetarian (eating only eggs milk and milk-derived products) are at risk (30). An important finding is that adolescents who have a borderline level of vitamin B12 develop signs of cognitive changes (31). B9 and B12 vitamins are efficient when used simultaneously in aged people. Vitamin B6 and B12 intakes are positively related to memory performance of middle-aged men and intakes at around RDI are associated with better memory functioning for women (32). For instance, in community-dwelling older women, significant vitamin B12 deficiency is

associated with a twofold risk of severe depression (33).

Supplementation with cobalamin improves cerebral and cognitive functions in the elderly (34). In fact, vitamin B12 levels should be measured in all elderly patients with behavioural disorders, because supplementation frequently improves the functioning of factors related to the frontal lobe, as well as the language function of those with cognitive disorders. However, supplementation is unfortunately not successful in the insane (35). In human, vitamin B12 must be given at the very beginning of the clinical signs, afterward it is non or poorly efficient (36). In human, pernicious anaemia is a sign of dementia and is associated with vitamin B12 deficiency (37). In fact, measurement of plasma homocysteine is a good marker of cobalamin and folate deficiency in patients with severely altered cognitive performance (38). In rats, vitamin B12 deficiency may play a role in neuronal degeneration through disturbance of polyamine concentrations in brain (39).

Practically no animal or higher plant possesses genetic material able to synthesise vitamin B12. In fact the cobalamins are exclusively synthesised by micro-organisms, bacteria, and yeasts. In human alimentation, vitamin B12 is exclusively present in food of animal origin: meat, eggs, shellfish, fish; and, to a lesser extend, cheese (notably compressed cooked cheese), milk and its derivatives. Cobalamine is nonetheless elaborated by a few vegetables but is poorly bioavailable (40), some algae seem to be the exception (41).

Vitamin C (ascorbic acid)

This vitamin plays many roles. Ascorbic acid also has a subtle influence on the elaboration and functioning of nervous tissue, among others. Its presence is required for the transformation of dopamine into noradrenaline. Moreover, the biosynthesis of catecholamines occurs in tissues rich in ascorbic acid like the brain and the adrenal gland. At very high doses, at least in the rat, vitamin C even has an anti-stress effect. In the elderly, ingestion of vitamin C is associated with a lower incidence of major alterations in cognitive performance (42). Others have reported a relationship between the serum level of vitamin C and the intelligence quotient: this increase by four points when the plasma concentration of vitamin C could increase by half. Indeed, some of the elements used in tests to determine IQ (non-verbal) are altered as a function of the serum concentration of vitamin C (43). Vitamin C and degenerative pathologies have been reviewed (44).

A regular intake of vitamin C reduces the risk of cataract (45). In fact, the vitamin plays an important role in protection against different harmful oxidation reactions that involve molecular oxygen. Its properties as a reducing agent and its reaction with oxygen-derived free radicals seem to be its most important biological functions.

Vitamine D

This vitamin is currently undergoing investigation in connection with the structure and function of the brain, since

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vitamin D or certain of its analogues are of interest in the prevention of various aspects of neurodegenerative or neuroimmune diseases (46). Vitamin D protects the neurones of the hippocampus (47), and modulates the transport of glucose to the brain (48). Its role in models of multiple sclerosis is under study as a result of recent positive findings, in particular concerning the duration and intensity of crises (49).

Vitamin E (tocopherol)

This vitamin protect especially against ageing, in particular the brain, notably in association with selenium. However, alpha-tocopherol also plays a role at the level of cognitive functions (50). In fact, what is known as vitamin E is in reality a mixture of numerous substances: tocotrienols and tocopherols (alpha, bêta, gamma, delta); moreover, alpha tocopherol has 3 asymmetric carbons, hence 3 different molecules. Each of these molecules is classically ascribed a coefficient of vitamin activity determined by various methods, either in vivo or in vitro. In terms of nutrition, only alpha-d-tocopherol - and not gamma-tocopherol - is bioavailable and integrated in biological membranes, including those in the brain (51). The eventual specific roles of gamma-tocopherol are currently investigated. Nutritional vitamin E deficiency alters brain fatty acid profile (52). Experimental vitamin E deficiency induces retinal abnormalities (53). In animal, early vitamin E supplementation in young but not aged mice reduces Abeta levels and amiloid deposition in a transgenic model of Alzheimer disease (54). High doses of vitamin E are proposed in the treatment of disorders of the central nervous system in the aged (55, 56) and using antioxidant vitamin supplements (including vitamin E) reduces risk of Alzheimer disease (56). The risk of dementia is significantly increased for the lowest vitmin E concentration compared to the highest one (OR=2.54) (57). Vitamin E may slow functional deterioration leading to nursing home placement (58). In general, at the molecular level, the tocopherols are extremely important. They have numerous roles, in particular they neutralise the active and toxic forms of oxygen and scavenge free radicals. That is to say, they protect unsaturated fatty acids against peroxidation, and thus contribute to maintaining the integrity and stability of cellular structures in the brain. They act in lipid phase at a very low concentration (about one molecule per two thousand fatty acid molecules) and take part in a vast complex and interactive protective system, in cooperation with beta-carotene, vitamin A, vitamin C, and various enzymes that function with selenium, copper, zinc, and manganese. A distinct clinical syndrome (with paralysis) of combined vitamin E and vitamin C deficiency have been described in guinea pigs (59). Interestingly, alternative non-antioxidant functions of vitamin E have been proposed and in particular of a "gene regulator" (60).

Tocopherols are found in very large amounts in certain vegetable oils, and also in eggs, a little in meat and tripes, without forgetting vegetables such as cereal germs and green vegetables (salads, cabbage, and spinach).

Vitamin K

Recently, it was demonstrated a correlation between vitamin K and sphingolipids concentrations in rat brain (61) ; moreover this vitamin present a protective effect on aging retina, the sparing effect being most evident in the inner plexiform layer and in the photoreceptor inner and outer segments (62). Assays with vitamin K remain to be made on human.

Minerals

The trace elements are present only in low but variable amounts. However, their physiological importance cannot be deduced by simple deduction from their concentration, even if it is low. Some, like iodine and cobalt, have only one main role. From among many candidates we will only examine iron, zinc, iodine, magnesium, and selenium.

Iron

Many symptoms have been reported to be clinical signs of iron deficiency, even in the absence of anaemia: for example apathy, somnolence, irritability, decreased attention, inability to concentrate, and memory loss. But these symptoms are difficult to interpret because of their subjective nature.

However, it is evident that iron modulates cerebral development (63), and the relationship between iron status and cognitive performance is currently attracting interest (64). The deficit in iron acts globally at two different levels: on one hand by less efficient supply of oxygen to the brain; and on the other by decreasing brain energy production, as iron deficiency decreases the activity of the enzyme cytochrome c oxidase in certain cerebral regions (65). This results in less production of energy because of the decreased activity of the enzyme, and consequently a decrease in metabolic activity of the cerebral cells. Iron deficiency during embryogenesis impairs myelination via the metabolism of oligodendrocytes (66). But all nervous cell types are affected, and as a result iron deficiency during early development perturbs cognitive functions in the long term, and this persists even after iron supplementation (67). It is unfortunately common to observe that severe iron deficiency during early childhood induces cognitive deficits that can persist after 10 years of treatment with iron (70). In fact, iron concentrations (and those of magnesium, copper, zinc, and selenium) are higher in the umbilical artery than in the vein, which makes them critical during the development of the foetus (68). The transfer of dietary iron to the foetus depends on its level in the mother's digestive tube (69).

Infantile anaemia with its associated iron deficiency is linked to perturbation of the development of cognitive functions (71, 72), and exists in school children and adolescents even in Western countries. It is important that iron deficiency be sought even in the absence of anaemia (73). In the domain of public health, the distribution of biscuits enriched in iron improves the intellectual performance of children in the underprivileged sector of the population (74). It should be noted that in some

countries iron deficiency can be due to loss of blood (and thus iron) caused by infection, particularly parasitic, leading to the same cognitive problems as nutritional deficiency of iron (75). Iron deficiency also causes perturbations in the electroencephalogram (76). The dopaminergic system may be especially involved (77), and this observation could be related to iron deficiency in children with attention-deficit/hyperactivity disorder (78). During aging, trace elements protect cognitive function (79).

Dietary iron exists in two main molecular classes according to criteria that satisfy both biochemistry and nutritional availability: heme iron and nonheme iron. An heme iron molecule was found in the brain, which is to be expected related to the oxygen requirements of that organ (80). Physiology enables human to absorb 25 to 30% of heme iron, but only 2 to 4% of that present in vegetables (mineral). Consequently, the human organism can take up one hundred times more iron (6 mg) in one hundred grams of the food richest in heme iron (cooked blood sausage) than in the vegetable food that is richest in heme iron (cooked lentils, 0.06 mg). The bioavailability of iron in a vegetable food depends on what is served with it. Thus, for example, a cup of tea drunk during a meal (and, to a lesser extent, coffee) decreases four-fold the amount of iron taken up by the organism, whereas a glass of orange juice doubles it. Animal proteins (of whatever source, terrestrial, maritime, aerial) increase the uptake of mineral iron, independently of whether they contain heme iron; on the other hand, soybean proteins decrease uptake slightly.

In France, the SU.VI.MAX study (81) showed that 93% of women of childbearing age ingest less iron than that advised in the RDA, 56.2% consume less than two thirds of the suggested amounts (82), 23% have totally depleted iron reserves, and 4.4% have a sufficiently severe deficit to result in iron deficiency anaemia – with the well-known accompanying difficulties and pathologies. In menopausal and post-menopausal women and in men, respectively 45.3% and 9.1% have iron levels below the RDA (83).

Copper

In brain aging and in neurodegenerative disorders, abnormal interactions of iron or copper with metal-binding protein, such as neuromelanin or amyloid-beta peptide (A β), leading to oxidative stress, are important mechanisms. An unbalanced copper metabolism homeostasis (due to dietary deficiency) could be linked to Alzheimer disease. In mouse, APP-induced alteration linked to copper homeostasis can be reversed by addition of dietary copper (84). Moreover, permanent impairment to motor function persists in rat after long-term recovery from perinatal copper deficiency (85).

Zinc

This element plays a role in cognitive development (86), and it also participates in the mechanisms for perception of taste and smell: a deficit induces anosmia. The sensory receptors and

brain regions that perceive and interpret the pleasures of eating are themselves very rich in zinc, and levels in the taste buds are very high, zinc is necessary for their function (87). Zinc acts by its presence in the gustin (88), which participate in the perception of taste. However, there is a danger that a vicious circle can be established which, unfortunately, is often met in elderly people: the low zinc level (due mainly to a decrease in the consumption of meat, finfish and seafood) leads to reduced appreciation of taste. Food seems insipid, and less is eaten due to the loss of pleasure – which increases zinc deficiency, thus the circle becomes even more vicious.

This metal plays a role in a multitude of physiological mechanisms. Interestingly, zinc deficiency impairs whole-body accumulation of polyunsaturated fatty acids (89), thus brain supplying could be affected. Part of cerebral zinc (10 to 15 %) is present in synaptic vesicles for some glutaminergic neurons (90). Consequently, zinc deficit induces behavioural changes (91). It has been suggested that some psychiatric problems can stem from the reduction in dietary zinc; animal experiments have shown clearly that deficiency (in particular during pregnancy) results in loss of neurones and a reduction in brain volume. In contrast, giving pregnant women zinc supplements has not been proved effective for improving the cognitive performance of their children (92).

Perinatal omega-3 polyunsaturated fatty acid supply modifies brain zinc homeostasis during adulthood, at least in rat, this being important in relation with the fact that neuronal zinc is involved in formation of amyloid plaques, a major characteristic of Alzheimer's disease; in fact, perinatal omega-3 deficiency induces overexpression of ZnT3 (transporter identified in synaptic vesicles and found in some regions such as cortex and hippocampus) and cause abnormal zinc metabolism in the brain (93).

Oysters are the food that is richest in zinc, they contain ten times more than the next richest foodstuffs, some cheeses, as well as steak and poultry livers. On the other hand, green vegetables, fruit, sugar, fats, and drinks are low in zinc.

Iodine

This trace element is directly involved in cerebral functioning and intelligence. In fact "cretin" was originally strictly a medical term, a consequence of the mental retardation in children due to iodine deficiency during pregnancy. Iodine is one of the trace elements present in the human body in extremely small amounts: 15-20 mg in the adult or 0.0285-10⁻³% of body weight. In humans, the only known role of iodine is to participate in the composition of hormones secreted by the thyroid gland. In humans, cerebral development takes place mainly during the foetal period, but it continues up until the end of the third year of life. Consequently, a deficiency of either iodine or thyroid hormones during this critical period induces not only a slowing of the metabolic activity of all the cells but also permanent alterations in the development of the brain, of which the most evident sign is

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irreversible mental retardation.

For example, thyroid hypertrophy due to low dietary intake of iodine affects numerous people in France (94). This can be dangerous when pregnant women are involved. In France, the prevalence of goitre (palpable thyroid) was 11.3% in men and 14.4% in women (95). Depending on the French region, ioduria below half the normal level, that is to say below 5 $\mu\text{mol}/100\text{ ml}$ (normal 10 μmol), concerns 7.8 to 22.7% of men and 14.2 to 30.2% of women.

The WHO internet site stresses that iodine deficiency is the first cerebral disease in the world that it would be possible to prevent. In fact, with goitre it affects 740 million human beings on earth. At Islamabad in 1994, an in-depth study showed that 40% of schoolchildren had goitre. At the general population level, iodine deficiency lowers IQ on average by 10 to 15 points (96). In some regions of India, endemic cretinism affects 3.5% of the population, 22% of children from 10 to 12 years have an IQ inferior to 70 (97). Iodine deficiency perturbs the intellectual and neuromotor functions even in apparently normal people (97). It is therefore recommended that iodine levels in pregnant women should be monitored to avoid possible intellectual problems in their children. In many countries, an insufficient intake is made worse by the consumption of vegetables rich in goitrogenic substances such as thioglucosides (like brassica) or the cyanoglucosides (manioc, sorgum, maize, sweet potatoes, etc.). In addition, salt used by the food-processing industry should be iodinated. Meanwhile, iodine can be found in useful amounts in mussels, oysters, seafood and eggs (2).

Magnesium

Its deficiency is usually linked to spasmodophilia, a state characterised by tetany without calcium being quantitatively low in the organism. The magnesium reserves (twenty-two grams in adults) are stored mainly in bone (more than half) and in skeletal muscle (one quarter). The rest is distributed throughout the organism, especially in the nervous system. It has two roles, structural and metabolic. It is a stabiliser of the different compartments of the cell (organelles, such as the nucleus, or the mitochondria that produce energy, etc.). Magnesium plays a role in all the major metabolisms: oxidation-reduction, ionic regulation, etc. It activates about three hundred enzymes. In animals, brain from magnesium deficient rats is more susceptible to permanent focal ischemia (99).

Magnesium participates in the formation and use of chemical links rich in energy that are the basis of all biological activity in the cell. Magnesium is indispensable both for the synthesis and action of ATP, and most enzymatic reactions depending on ATP require magnesium, whether for carbohydrate, lipid, nuclear, or protein metabolism. Magnesium deficiency concerns up to one fifth of the french population: 18% of men and 23% of women have intakes lower than 2/3 of the RDA; 77% of women and 72% of men have intakes lower than the

RDA (100). Magnesium intake is generally directly correlated with calorie intake. This is because most foods rich in magnesium also have high calorie content, among the various possible sources, the magnesium in water and milk occupies a privileged position. It should be noted that milk is richer in magnesium than the high-magnesium mineral waters, in addition its bioavailability is excellent. Other foods in order of decreasing magnesium content are: whelks, winkles, snails (five times richer than oysters), haricot beans, walnuts, sorrel, lentils, mussels, spinach, beetroot (2).

Selenium

In the brain, only about 15% of this important trace element is expended in its association with glutathione peroxidase, a crucial enzyme for protection against peroxidation. The role of the remaining 85% still remains to be elucidated. In fact, major neurological dysfunction occurs in mice with targeted deletion of selenoprotein P gene (101). There is also a special glutathione peroxidase in the brain that is sensitive to vitamin E, and which directly protects membrane phospholipids (102). At least in animal models, selenium deficiency alters neurological development. Selenium is found in few mushrooms (cepes), finfish and animal seafood, some tripe products, mussels, oysters, eggs, and fish.

Other trace elements

Although known to modulate carbohydrate metabolism, chromium effect have not been studied in the nervous tissue. The importance of cobalt is illustrated by the role of vitamin B12 (a cobalamin) in the nervous tissue. The importance of lithium in psychiatry is known for a long time, acting notably at the level of neurotransmitters and phospholipids metabolism. The molecular mechanisms of biological effects of lithium are complex and not totally elucidated, the phosphoinositides deficiency due to inositol depletion being not the only mechanism of lithium action in brain: inhibition of 5HT autoreceptors, anti-apoptotic action, inhibition of glycogen synthetase kinase-3, RNA processing, glutamate reuptake, are also speculated among others. Although essential, manganese is also known to be toxic. A deficiency in molybdenum has been tentatively associated to neurological alterations.

Conclusions

Non essential micronutrients are also involved in the brain functions. They consist principally of substances whose main quality is their antioxidant activity. Increased levels of oxidative stress and/or antioxidant deficiencies may pose risk factors for cognitive decline (103). Like vitamin C, the carotenoids may reduce cognitive loss during ageing (104). Extracts of ginkgo have also been reported to be effective (105). In general, the role of antioxidant micronutrients is probably important during the course of Alzheimer's disease (10). In this setting, wine polyphenols, together with alcohol

itself, have the reputation of providing some protection against dementia and Alzheimer's disease (106, 107). For example, apple juice prevents oxidative stress and impaired cognitive performance caused by genetic and dietary deficiencies in mice (108). Interestingly, frontal lobes, but not occipital lobes, exhibit an age-related decline in retinol, total tocopherols, total xanthophylls and carotenoids (109). Two carotenoids that are not precursors of vitamin A, lutein and zeaxanthine which are found in numerous vegetables as well as in egg yolk, can reduce the risk of cataract (by 20%) and macular degeneration due to age associated with visual loss (by 40%), because the retina is particularly rich in these substances (110).

Nutrition is an important determinant of human mental performance. Especially during aging, dietary compounds prevent or delay age-related cognitive impairment, which is known to result from changes in the diet, whether they are short term (breakfast in the morning), middle term (iron to ensure oxygenation) or long term (fatty acids changing brain structure and functions). At a time in history when prevention has been raised to a kind of existentialist philosophy, it is strange that people are not prudent enough to eat the necessary simple foodstuffs to ensure a satisfactory supply of nutrients for the body and guarantee the proper functioning of the brain. In fact, SU.VI.MAX, a large epidemiological study carried out in France, gives information simultaneously for the whole country concerning peoples' state of health and what they are eating. It shows that a large fraction of the French population ingests less than 2/3 of the amounts proposed for vitamins and minerals in the recommended nutritional intakes (Table 1). The world of "functional foods" (111) (new appellation for the "nutraceuticals") must henceforth include the brain as an important research target.

Table 1

Percentages of french volunteers whose intake is less than 2/3 of the French recommended dietary allowances (RDA)

	Women	Men
Vitamin E	38.0	18.7
Vitamin B1 (thiamine)	25.8	18.1
Vitamin B2 (riboflavin)	7.1	5.6
Niacin (B3)	9.4	4.0
Vitamin B6 (pyridoxin)	36.2	16.0
Folic acid (B9)	20.6	8.3
Vitamin B12 (cobalamin)	2.7	0.6
Vitamin C (ascorbic acid)	27.4	17.4
Calcium	16.4	8.2
Magnesium	19.0	Nd
Iron	45.1	1.0

(From 83). SUVIMAX, results of 1998. Based on 1992 french RDA. More than 13 017 volunteers throughout France: women, 35-60 years; men 45-60 years.

Dietetics can no longer limit itself to outlawing poisons and contaminants. Veritable dietary security consists in finding in foodstuffs the nutritional elements they contain (the nutrients), and which at the same time give pleasure. Food safety must not limit itself to weeding out poisons and contaminants. True food safety consists in finding foods that contain nutritive substances (nutrients) and at the same time give pleasure. This principle is true for all populations, whether they belong to the overprivileged or underprivileged world, because both are threatened. True food security consists in having access to the whole diversity of nutrients, as dietary habits impacts on the human brain and feelings: "tell me what you eat, and I'll tell you what you are". So what strategy should the brain and its intelligence pursue? A good dietary regimen. By what tactics can this be achieved? By combining foods. How? With appetite!

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