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Nutrition, Skin, Brain

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Summary
In the present paper we report on the relationship between nutrition, skin and brain. Biochemical indicators that are crucial for the optimation of function and structure of membranes of both receptors and all other cells, are evaluated, with particular attention to Dodosahexaenoic acid (DHA) and Arachidonic acid (AA). Through a synthetic overview of nutrition changes occurred from prehistory to the present, the aim of this review is to broaden the knowledge (still limited) of the relationship between nutrients and brain so that to be able to identify the key aspects that connect nutrition to brain functions.

Key Words
Skin; Brain; docosahexaenoic acid; arachidonic acid; nutrition changes.

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Introduction

A constant malnutrition, psycho-social stress and bad eating-habits are concomitant and/or decisive factors of many situations of risk for the health. A status of poverty and uneasiness is responsible, along with other events, of the development of poverty-related diseases, nearly unknown to us today. The skin becomes the centre of attention in its visible expression of biochemical and molecular phenomena and in its ectodermic embryonic origin. The brain too needs in-depth analysis. In the context of several issues concerning the "Human Mobile Population", we report herein on relationships between human nutrition, skin and brain to define those rules made up to ensure welfare to all human beings, especially the weakest and poorest ones.

Nutrition, Skin and Brain: evaluation of biochemical nutritional indicators for the optimisation of the function and protection of the membrane

Skin and brain can be considered the most complex organs of the organism for many reasons: for their important biochemical-functional properties, for being organs exposed and connected with the outside, for their selective characteristics and for the fact that they have a limited Desaturases activity, which does not allow an efficient production, at local level, of long-chain polyunsaturated fatty acids of Omega-3 and Omega-6 series. They are, therefore, in close dependence with the nutritional event regarding both metabolic processes and protection from oxidative damage.

The skin lipid metabolism, as well as the interpretation of its anomalies, represents one of the most complex chapters both at diagnostic and therapeutic levels, compared to many other tissues or body systems. In the absence of a biochemical diagnosis of the lipid composition of skin and brain, many studies have been done on the role of platelets as "ambassadors of the brain", see Takahashi (1976), Marangos et al. (1980), Kim et al. (1982), Dreux & Launay (1988), Wirz-Justice (1988), Plein & Berk (2001), Maurer-Spurej et al. (2007), and Cocchi et

al. (2012). However, it is to underline that any intervention may be meaningless if a fundamental point is neglected, that is, ensuring cellular homeostasis is extremely important for better efficacy of therapeutic intervention, or, at times, may be decisive itself for a prompt recover.

Only through a careful use of certain nutrients, and within limited extends, it is possible to check the status of the membrane both in its functional expression and pathological manifestations. Scientific papers on this subject are numerous and influential. It is important to encourage a new level of diagnostic and therapeutic knowledge based on the development of new and sophisticated analytical techniques. For example, it is possible to investigate about plasma and blood cells or skin lipids by identifying all organic structures that guarantee functional cellular homeostasis (Passi et al., 2001a, b; 2002; 2003a, b). Hence, it is possible to estimate:

PLASM	- Vitamin E; Vitamin A; Beta-carotene; Lycopene; $CoQ10H_2$; CoQ10; Ascorbate; Urate; Thiols; Carbonyls (proteins); - Fatty acids of triglycerides and phospholipids; - C18:2/(C20:3+C20:4) rate to assess Delta6-Desaturase activity.
ERYTHROCITES	- SOD; GPX; CAT; GSH; GS-SG; vit. E; $CoQ10H_2$; CoQ10 - Fatty acids of membrane phospholipids; - Fatty acids *Trans* (AA and DHA)
LYMPHOCITES	- Vit. E; $CoQ10H_2$; CoQ10 - Fatty acids of membrane phospholipids - Fatty Acids Trans (AA and DHA)
PLATELETS	- Vit. E; $CoQ10H_2$; CoQ10 - Fatty acids of membrane phospholipids

For these reasons nutrition can and must play a strategic role since it is the only way to ensure the physiological balance of the biochemical functions that modulate the processes of metabolic protection, regulation and mediation. Modern nutrition, therefore, is strictly connected to clinic. Unlike in the past, it may now face - beyond the visible level - the microscopic one as it intervenes, at the cellular level, during diagnostic, prognostic and therapeutic phases. In fact, nutrition can be considered as a discipline that, joined to the most sophisticated means of investigation, may help in interpreting clinical pathology of membranes, which is ultimately the only way to ensure the maximum effectiveness of any therapeutic intervention.

Nutrition and Brain. Docosahexaenoic acid (DHA), arachidonic acid and Brain: an overview

The major polyunsaturated fatty acid in the mammalian brain is docosahexaenoic acid (DHA). DHA is mainly localized in the gray matter and more specifically in phosphatidylserine (PS) and phosphatidylethanolamine (PE) fractions. A small amount of DHA is contained in the phosphatidylinositol (PI) that is rich in arachidonic acid (AA). DHA is concentrated in neurons, in synaptosomes, particularly in nerve membranes, and in sinaptosomal plasmatic membrames and synaptic vescicles. Myelin and white matter contain rather limited amounts of polyenes.

When comparing different animal species, DHA is always particularly abundant in the brain.

Drastic reductions of DHA in the brain can be determined as a result of depletion of omega-3 in an early stage of postnatal development, or during pregnancy, or, even, through several generations; this condition leads to severe depletion of DHA in neurons, astrocytes, terminal nerves and myelin.

There is, however, a mechanism for replacement with n-6 fatty acids, in case of deficiency of omega-3. This mechanism of adaptation aim sat keeping the level of polyunsaturate fatty acids (PUFAs) constant in the brain. If both (i.e. n-3 and n-6) sets are deficient, it is formed 20:3,n-9 which accumulates in brain lipids, particularly in the aminophospholipids. Hence, the presence of 20:3,n-9 (Holman triene) is a sign of PUFAs deficiency.

One of the most important questions, particularly in humans, is whether n-3 fatty acids are required for a normal function at cellular, organ or even organism level. Although this question has not yet found a definitive answer, it is possible to evaluate data available for different types of biological/functional alterations (for example, neurological degenerations).

Menkes (1998) described a disease known as Kinky hair disease, characterized by cerebral and cerebellar degeneration, severe and early neurological damage and mental delay, shown by the very first months of life. Lipid classes and distribution of fatty acids were normal in the brain of these babies (post-mortem biopsies), while DHA was significantly decreased in PS and, sometimes, in PE fractions.

A selective loss of DHA in combination with a severe neurological disease, may indicate that neur-

onal degeneration occurs as a consequence of the scantiness of this fatty acid.

Loss of DHA has been associated with many other abnormal or pathological conditions. Protein malnutrition and a severe shortage of threonine and lysine determine a decrease of DHA in the early stage of development. In four patients with Neuronal Ceroid Lipofuscinoses became evident a decrease of DHA in platelet glycerolipids. Other authors have described a progressive encephalopathy, showing a drop of DHA and an increase of AA.

In old men up to 60 years, there is a decreasing trend of accumulation of AA and DHA in the brain, PS district, while the opposite occurs in PE, up to about 40 years; this phenomenon becomes reversible after the 60th year of age. Neuroblastoma cells, in vitro, loose their ability to form PUFA with the increase of cellular divisions (Salem et al., 1986).

Mode of action of arachidonic acid and DHA on cellular activation

The effects of arachidonic acid may be classified in accordance with direct actions, actions mediated by Protein Kinase C, by lipo-, cycle- and epoxy-derivatives and by the formation of free radicals.

The effects of DHA are accomplished through the modification of [Ca_2^{++}] and the formation of intracellular inositol phosphates, influencing the levels of cyclic AMP, modifying the activity of enzymes related to intracellular signaling systems such as Protein Kinase C (PKC), altering production of the Platelet Derived Growth Factor (PDGF), early gene expression and, perhaps, some mechanisms of cell growth.

It can be assumed that both fatty acids (DHA and AA) can be considered as intracellular secondary messengers, as they modulate signal transduction.

Others Authors have described a decrease of total PUFAs in patients with multiple sclerosis (Swank, 1950; Baker et al., 1964; Belin et al., 1971; Tichy & Vymazal, 1973; Love et al., 1974). The white matter, apparently normal, of patients with multiple sclerosis had less DHA compared with controls, but demyelinated tissues had twice as DHA and AA compared to controls. These findings seem to suggest that multiple sclerosis may be related to a lack of omega-3 in the early stages of development.

Additional evidence of a possible role of DHA in brain function comes from studies of abnormalities of brain conditions such as those that occur in anoxia or ischemia. For example, a pre-treatment with DHA can reduce the neurological deficit and downsizes the area of infarction after ligation of the left middle cerebral artery in the cat. Finally, AA and DHA are released by brain and retinal lipids after shock or anoxia.

From Prehistory to date: nutrition changes

The unequivocal proof of the dependence of man from nature comes by the essentiality of some nutrients without which the body cannot exist, grow or reproduce. Even energy is essential under certain aspects: without it, in fact, the body could not live, although provided with all essential nutrients. If the energy is not adequate to the type of activity, the human body would succumb in a relatively short time.

The relativity of human knowledge - which is, sometimes, replaced by intuition - is given by the different attitude of man in living and interpreting phenomena. For what may seem a curious design, after millions of years, man has undergone an acceleration of events that, in some decades, led him to better understand himself and made him able to rationally choose food, according to its composition, to dispose then of its use to find a progressive optimization of biological functions. What man now does with a greater degree of awareness and rationality, just over a century ago was on his instinct, that is, that complex phenomenon that allowed the survival through the act of eating and where the nutritional choice was the result of a selection of food once, by experience, he could assume and identify its role for the body.

The lowest level of knowledge required an intellectual commitment considerably higher than today in the race for survival.If we compare the different eating patterns from prehistoric times to today, we realize that a fundamental fact differentiates them: the quality and quantity of fat consumed, considering their characterization in fatty acids. We know only since 1936 that some of these are essential (Burr & Burr, 1929): linoleic acid and alpha-linolenic acid, and that some of their derivatives, such as arachidonic acid (AA) and docosahexaenoic acid (DHA), play a decisive role in the functionality of biological membranes in general and, particularly, of membranes of brain and nerves (Noble & Cocchi, 1990; Cocchi & Noble, 1992; Cocchi et al., 1993; Maldjian et al., 1995; Cocchi & Turchetto, 1999).

At this point it seems easy to imagine that increased intake of DHA and AA during the nutritional unconscious phase of man could be a forced phenomenon (Crawford, 2006, 2010, 2012; Venturi & Venturi, 2014) replacing, as pure biological event, the

not yet completed evolutionary process of the brain that starting from needs and environmental interactions, got to understand phenomena, explain them and, as a consequence, determine food choices. As if a more "primitive" (as to say so) brain had had more opportunities to use valuable nutritional sources, in contrast to a "modern" brain characterized by a more efficient brain-training, wider cognitive potentials, and showing a still important but minor "appetite" for AA and DHA.

However, we must not forget the metabolic activity of lipids during the development of fetus and placenta. Numerous studies both in man, and animals (eg. chicken embryos), showed a greater amount of LCPs in fetal organisms with respect to the mothers; this is clearly thanks to a process of bio-magnification, from placenta, through liver to fetal brain, which is very similar to that found in chickens, from the yolk sac, through the membrane of the yolk sac, to liver and embryonic brain (Cocchi & Noble, 1992; Cocchi et al., 1993).

On this basis, the "aquatic" theory, linked to the need to have important resources of n-3 fatty acids, seems to be likely. It should not be, however, forgotten that the crucial phase of maturation of the brain in perinatal age has autonomous resources of intake of long chain fatty acids (AA and DHA) from precursors (linoleic and alpha linolenic acid), related to the activity of transformation occurring in the placenta. This activity, of course, has always existed, otherwise the impossibility of continuation of the species.

Another hypothesis may also be the one that sees in the evolution of nutritional process, the progressive use, or rather, the gradual availability of nutrients to strengthen and sophisticate, with complementary actions, the complexity of biochemical and synaptic functions, and of neurotransmission, so as to reduce the demand for some nutritious rather than others.It is known, in fact, that in modern alimentation there is an abnormal prevalence of n-6 lipids, relative to n-3. Although without any apparent and obvious undesirable events, this issue is directly related to eating habits and conditioning of the food industry, which has, however, shown a new level of alert to this problem. To give the sign of concern, there are many scientific works that contribute to draw the attention to the recovery of certain levels of omega-3 in the diet.

It cannot be neglected the fact that, despite stillbirths decreased, the number of children with mental and developmental defects of vision did not follow this trend. Not much is known about the causes of the increase of neurological disorders in low-weight infants. Retinopathy was attributed to an excess of oxygen and severe deficiency of vitamin E, while the cerebral palsy to a lack of oxygen (asphyxia) at birth. Both of these interpretations are now in question because of a non-precise correlation between causal event and damage. In humans, the brain retains biological priorities during fetal development, with a heavy investment on biochemical lipids required for membrane bilayers. It should be remembered that essential fatty acids determine brain development and integrity, as well as the integrity of the vascular system. Many researchers argue that the intake of fatty acids is not able to correct certain pathological phenomena. Probably, at present we still do not know or do not want to give the right importance to bio-regulation, a biochemical phenomenon from which derives the opportunity to make informed (nutritional) choices for the optimization of functional activities and prevention of diseases.

It is necessary to stress once again that the pharmacological culture should be reconsidered on the basis of nutrition and biochemistry, also to bar the way to a wrong pharmacological use of nutrients with speculative purposes, but we must also say that the proper use of medications, now that the receptor theory is documented and proven, should interact with nutrition. Indeed, it may facilitate an efficient response to the treatment, the optimization of membrane functions (also in receptors), the best utilization of the drug and the maximum reduction of its potential toxicity. Thus, there is the possibility to reduce drug doses and to prevent drug misuse.

Matter, Man and Brain between thory and scientific certainty

Almost all are fascinated by the creation of matter, from that random or premeditated combination of elements that gave rise to the rocks, such as silicon and oxygen, or water, such as hydrogen and oxygen, or to the whole organic or inorganic world characterizing life or habitats life depends on, that is carbon and its metabolism, or nitrogen and its metabolism.

But only few however think, as a decisive condition, to the molecular construction that beyond any other element or substance essential to life, does determine architecturally life itself: the cell membrane with its phospholipid bilayer, hydrophilic and hydrophobic at a time, constituting the watershed that allows the character and shape of animal organisms.

From microscopic to submicroscopic level, cell membrane, mitochondrial membrane, microsomal, liposomal, receptor membranes do regulate all life processes by the architecture in specialized lipids

and, more in particular, the composition in special fatty acids. These fatty acids have a place in the biological evolution of the brain, but, above all, as a sign of the very close connection and interdependence between man and environment, it has to be reminded that they come from food.

The human brain has no comparison in terms of capacity, size and complexity compared to the other species of animals. The flow of ions and electrical informations, constant and relentless, is the guarantee of life of the brain; through a complex system, made of trans-membrane transports, strongly dependent by the mediation of structural lipids, the brain is the center of all those functions that affect life from the physical, mental and behavioral standpoint, in a perfect interaction between the genetic determination of the individual and his social relationships.

In amphibians and marine mammals photoreceptors use DHA as the main fatty acid included in membrane phosphoglycerides; synaptic membranes involved in the transduction of signals use high proportions of DHA; in another lipid fraction arachidonic acid prevails; during its embryonic development the brain is particularly rich of DHA and AA, In most animal specie, reproductive cells recognize DHA as a critical element in membrane composition. Briefly, the number of carbon atoms and double bonds, therefore, represent one of the biological events extremely important for structure and function of very specialized cells.

Because comparative biochemistry has shown that there are not substantial differences in the fatty acid composition of animal species, even if their development is different, it remains to understand whether these fatty acids are, compared to the brain, essential conditioned, or represent limiting stages, or still are species-specific conditioning elements within the network of substances that determine and maintain the cellular functions of the membrane. In practice, it remains to be established what is the message inscribed and perpetuating with the animal species whose properties are reflected in the metabolism of polyunsaturated fatty acids. Several lines of evidence and assumptions indicate that the brain as well, as photoreceptors and nervous system, needs marine nutrients (especially DHA) for its growth, both in a functional and protective (antioxidants) sense.

The animal species of the savannah possessed a brain lacking of DHA, but rich in arachidonic acid.

After the discovery of essentiality of some polyunsaturated fatty acids, as linoleic and α-linolenic acids, we can assume that animal organisms use the biological evolution of the enzyme systems, to ensure, beyond survival, the functional capacity that makes the difference, compared to other animal species. Recently, Linoleic Acid has been reported as a crucial element for the stability of the brain as well as the most critical factor in Mood disorderd and in ischemic heart disease (Cocchi et al., 2004; Cocchi et al., 2013; Cocchi et al., 2014; Benedetti et al., 2014; Cocchi & Minuto, in press.).

An important chapter in the study of the relationship between the functional architecture of membrane and mechanisms pathological conditions probably, has to be developed by investigating on membranes and/or structure of receptors. One may think that we know what are the optimal bio-conditions to ensure the best functional outcome of membranes with the maximum metabolic efficiency; one may think that, from a structural standpoint, as it has been demonstrated, biological mechanisms are the same for everyone. However, we cannot explain, nor even predict, for example, among all children suffering from the same shock due to a lack of oxygen, which one will manifest serious harm and, later, will suffer from spastic attitudes and/or auditory, visual or mental handicaps. In our opinion, the possibility of predicting disability after birth, when implications of genetic nature are excluded, might be investigated in biological materials available during pregnancy, with particular attention to maternal and fetal lipids.

It is possible that qualitatively the organic membrane structures are unchanged but that small changes during the phase of rapid development of fetus determine abnormalities, even irreversible. It is also conceivable that the membrane damage is localized at the receptor level and that this event affects the network of cellular responses in (apparent) normal conditions as well. It still remains to be established, definitively, whether the pool of maternal nutrients bioavailable for the fetus, if not sufficient, might be responsible for the negative effects on fetal and neonatal development. Unfortunately, research in pregnancy is still insufficient in this respect and still too tied to the observation of the consequences and not of the biochemical causes, to address this item.

Nutrients and Brain

Having a still limited knowledge about the brain, and looking at it with a degree of respect and subjection, led us to think of it almost as a superior entity capable of total independence in the maintenance of its functions, powered by a self-production of energy. It is true that, when considering the extraordinary complexity of its activities, the brain shows, with re-

spect to its basic nutritional needs, a level of great simplicity. Glucose and ketone bodies, in addition to oxygen, are the most basic units which guarantee the flow of energy necessary to support brain cellular activity. What is able to modify these items preventing the performance of their metabolic activity, can result in injury or damage, even irreversible, to this precious organ.

The most elementary level of nutrition guarantees the more complex one which is made of perfect mechanisms of chemical, biochemical and nutritional interactions affecting the transfer of stimuli, selection of responses, adaptation to environmental changes, and also the whole of the neurochemical changes resulting in feelings, that are not easy to understand even for those who are friendly with scientific knowledge. So it happens, in case of damage to the first level, a devastating effect that can damage the individual, in physical functions, and even in his partial or total capacity to be a conscious being (including thinking and feeling). In case of damage to the second level, such damage is a kind of "selective", including neurotransmitter modification, synapsis interruption, or receptor modification etc., and, generally, it affects those features that conventionally we define feelings or personality, causing a devastating, partial or total effect, leaving intact the body and cancelling, instead, what is universally known as the "dignity" of man.

For a long time dietary sources of energy, plastic elements and bio regulators were thought to be unimportant for the brain, believing it capable of reactions, but also of autonomous selective synthesis of nutrients for its own needs. Today we can re-consider these convictions. In fact it is known that the synthesis of neurotransmitters is not that autonomous and that the rate of production of serotonin, catecholamines and acetylcholine, is dependent by the fluctuating dietary intake of tryptophan, tyrosine and choline.

These substances respond, in their bioavailability, to quality and quantity of food consumed. On these fundamental observations flourished, in 70–80s, authoritative literature proposing the use of nutrients in the treatment of certain diseases of the brain, or to treat, by special diets, inborn errors of metabolism that can compromise, for example, a proper brain development and maturation in newborns. A still valid consideration is that, generally, an "immature" brain and nervous system are more sensitive to dietary changes than a mature and adult brain and nervous system. We must assume, however, that, although the mechanisms of synthesis of neurotransmitters (i.e. those substances that play a crucial role in the functioning of the nervous system, as well as on other functions) are dependent by biochemistry of essential nutrients, on the contrary, it is not true that these substances are able to repair damages which can be created by specific pathologies. This means that the attitude in nutrition for the body in general and the brain in particular, must be to guarantee a rational use of nutrients, to determine their most effective use in order to maintain the biological functions at the highest levels of efficiency.

In compliance with this concept, follow the benefits that can be quantified in: i) a better capacity of the organism to respond to a pathological event; ii) slowdown of functional deterioration; iii) a better control of those environmental cues that can produce negative effects.

This is especially true for the brain where, unlike other organs, the right balance of functional activities is responsible for a quality of life that involves the individual and his "social life". Moreover, some experiments conducted in the 70's by prof. O.M. Olivo on in vitro cell increased metabolism and repaired cellular activity induced by nutrients (determined and evaluated by the technique of breathing) highlighted the extraordinarily important role played by nutrition on the control of phenomena that are crucial for the efficiency of organic structures and, then, for the proper performance of the vital phenomena and protection against pathology (Cocchi et al., 1979a, b, c; 1980).

In this sense, one of the authors [Cocchi] strongly supported, in the last few years, the importance of the effect exerted by specific fatty acids, i.e. DHA and AA, derived from dietary and metabolic pathways, in the optimization process of nerve functions through the mechanisms of regulation of the membrane of the brain cell, in particular during the step of chemical maturation of the brain at perinatal age.

In conclusion, three key aspects, therefore, connect nutrition to brain functions; i) energy as a global phenomenon that allows the brain activity; ii) specific nutrients that regulate the synthesis of neurotransmitters; and iii) specific nutrients that regulate the functions of the membrane. For this reason we can say that nutrition participates in the elaboration of the vital message from its most intimate chords.

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