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Multiple facets of membrane lipids and the diversity of their action mode with special emphasis on the central nervous system

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Abstract – This issue of *Reproduction Nutrition Development* was scheduled along with 8 papers on the metabolism of polyunsaturated fatty acids (PUFAs) and their physiological roles within the central nervous system. Topics focused on PUFAs from the n-3 series, especially on docosahexaenoic acid (DHA) which is particularly abundant in the cell membranes of brain and retina. Reviews and original articles emphasize the impact of n-3 PUFAs on the physical properties of membranes, the neuroprotective mechanisms via Ca^{2+} signalling in astrocytes, the n-3 status of infants suffering of Attention Deficit Hyperactivity Disorder (ADHD) and the mental development of neonates in relation with maternal feeding. The DHA metabolism in humans and its endogenous production from alpha-linolenic acid is reviewed. Besides, it is described and discussed how the generation of PUFA-derived mediators is modulated by the retinoic acid-receptor signalling via activation of cognate phospholipase activities. The sensitivity and recovering of neurons to oxidative stress is also addressed in this volume, through the description of a model of iron-induced injury in the rat brain. The diversity of these 8 articles illustrates the multiple roles of PUFAs within the central nervous system.

arachidonic acid / astrocytes and calcium signalling / Attention Deficit Hyperactivity Disorder / central nervous system / docosahexaenoic acid / endogenous conversion / membrane physical properties / milk and infant mental development / omega-3 and omega-6 fatty acids / oxidative stress / phospholipases / raft / retinoic acid

1. INTRODUCTION

This part of volume of *Reproduction Nutrition Development* is devoted to several facets of the functional roles of fatty acids and to their metabolism within the nervous system. The multi-disciplinarity of the topics covered within this issue reflects the extraordinary diversity of the regulation pathways in which fatty acids, especially

the polyunsaturated fatty acids (PUFAs), are closely implicated, either directly as membrane components or indirectly as precursors of active metabolites. Probably, there is no other example of nutrients that cumulate the particular features of being indispensable components of membrane genesis, modulators of the membrane dynamics and transmembrane functions, and being at the same time endogenous mediators in

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cell signalling and gene expression. These multiple features of PUFAs – which are not mutually exclusive – underlie the adequate perinatal development of the CNS, contribute to protect the brain from pathological stimuli, and finally participate in the behavioral functions throughout the lifespan [1, 2].

Starting with the molecular scale, the article by Stillwell et al. [3] shows that docosahexaenoic acid (DHA, 22:6n-3), the longest and most unsaturated fatty acid found in membranes, is incorporated into the different phospholipid molecular species according to a tissue-specific distribution. It is consensually recognised that the concentration of DHA affects the physical properties of membranes, but generations of researchers have debated, and still debate, on how. Stillwell et al. offer an overview of the means by which DHA modulates the membrane architecture and physical properties, through the complementary and evolutive notions of membrane curvature, fluidity, deformability, microdomain organisation and rafts. In particular, it is explained in this article how the interactions between DHA and cholesterol, which produce opposite effects on the lateral partitioning of ordered and disordered domains, may affect the membrane structure and hence the properties of the embedded proteins. From this view, the most thoroughly studied of the integral membrane receptors by far has been rhodopsin. The concept has emerged that the photo-induced conformational changes of rhodopsin are primarily enhanced by DHA-rich phospholipids and secondarily slowed down by cholesterol [4]. This model probably provides the most comprehensive molecular basis of the mechanism by which the DHA status may be related to the development of the visual function during infancy.

One important challenge in human nutrition is the question of whether the brain obtains its DHA directly from dietary fats, body stores, or endogenous conversion of the n-3 dietary precursor, α -linolenic acid (18:3n-3). The question of the conversion

pathway is addressed by Burdge and Calder [5] who reviewed recent studies that have been conducted in several countries. Adult men and women volunteers had received tracer doses of a stable isotope of α -LNA, enabling the investigators to examine the short-term metabolic fate of α -LNA, that is either storage, oxidation or conversion into the major long-chain derivatives, eicosapentaenoic acid (EPA, 20:5n-3) and DHA. Both the short-term studies using stable isotopes and the more traditional long-term studies of dietary intakes indicate that α -LNA is a limited source of long-chain derivatives in adults, especially with regards to the production of DHA and its incorporation into the bloodstream lipids. More surprisingly, the fractional conversion of α -LNA appears to be greater in women than in men, raising the unresolved question of the possible role of sex steroids in the regulation of PUFA metabolism. In any event, one important conclusion brought about by the review of Burdge and Calder is that adequate intakes of preformed DHA could be more efficient than intakes of α -LNA for maintaining optimal tissue functions throughout adult life.

The impact of long-chain PUFAs on health, especially on mental health, increasingly appears of capital importance. Altered levels of PUFAs in blood lipids have been reported in a variety of neuropathologies, and several epidemiological studies have shown that frequent consumption of n-3 fatty acids may be inversely linked to neuropsychiatric and neurodegenerative diseases [6, 7]. Although the causes of the observed abnormalities of fatty acids in sufferers of neuropathologies are mostly unknown, it is considered that normalisation of the PUFA status through dietary supplementation could be beneficial to prevent these diseases or could help improve the cognitive and behavioral functions. This nutritional approach is proposed by Young et al. [8] who specifically addressed in their article the Attention Deficit Hyperactivity Disorder (ADHD), a neuropsychiatric disease that is commonly associated

with decreased blood n-3 fatty acid levels. In particular, ADHD patients present a higher ratio of arachidonic acid (AA, 20:4n-6) to EPA than normal. The objective of Young et al. was to raise the levels of the long-chain n-3 polyunsaturated fatty acids in the serum phospholipids of adults with diagnosed ADHD, and thereby to decrease the AA/EPA ratio. As discussed in connection with the review by Burdge and Calder [5], Young et al. examined whether intakes of flax oil rich in α -LNA can be as much efficient to raise the n-3 status of ADHD patients as using fish oil rich in DHA and EPA. Their data indicate that treatment with fish oil increases the EPA and DHA levels and decreases the AA/EPA ratio [8]. The effect of flax oil on EPA and DHA being of very low extent, the actual metabolic ability of ADHD patients to convert α -LNA into its longer-chain derivatives should be questioned. Clearly, this original study shows that if the n-3 PUFA status needs to be optimised in ADHD patients, fish oil will be much more efficient than vegetable oil.

The PUFA status also results from the whole energy and lipid metabolism. Since dietary fats are generally composed of blends of saturated, monounsaturated and polyunsaturated fatty acids, Rioux et al. [9] examined the impact of dietary myristic acid (14:0) on the PUFA levels within rat tissues. They show that physiological intakes of 14:0 produce an increase of the PUFA contents. PUFAs from both the n-6 and n-3 series increased, but this effect only affected fatty acids made of 20 carbons [9]. Hence, dietary myristic acid may participate in the regulation of PUFA metabolism, especially those serving as potential precursors of bioactive metabolites (eicosanoids). This nutritional aspect is important since, once incorporated into neuronal membrane phospholipids, PUFAs are susceptible to be released under the action of hormonal stimuli and to generate an array of mediators that may trigger a cascade of events [10]. Thereby, the enzymatic release of PUFAs from membranes constitutes a key process in cell signalling, that has an impact on cell

physiology, growth, differentiation, or apoptosis. Lipid signalling is reviewed or addressed in three studies within the present volume.

The commentary article by Farooqui and Horrocks [11] focuses on the role of phospholipases in the release of lipid mediators which are implicated in the differentiation commitment of neuronal cells. The authors have particularly studied the coupling between the activation of phospholipases and the retinoic acid receptor-mediated gene transcription. The retinoic acid receptor pathway is known to activate genes involved in lipid metabolism [12] and to stimulate morphological differentiation of neuronal cells [13]. Their striking conclusion is that retinoic acid increases the transcription and thus the activity of nuclear phospholipases, resulting in the hydrolysis of nuclear phospholipids without an effect on non-nuclear membranes. Farooqui and Horrocks suggest that the nucleus controls through the phospholipase pathway the redistribution of AA from nuclear phospholipids into other cellular membranes. Thus, nuclear membrane phospholipids are substrates of phospholipases specifically operating within the nucleus for the release of AA and diacylglycerol (DAG) and for the generation of AA-derived mediators. These metabolites are normally involved in cell proliferation and differentiation. However in pathological conditions of overproduction, they may trigger inflammatory, oxidative and neurodegenerative processes.

The release of PUFAs from astrocyte membranes is induced by different phospholipases, most of the AA release being stimulated by Ca^{2+} while that of DHA is Ca^{2+} -independent [14]. Therefore, the release of Ca^{2+} from its internal stores plays a crucial role in the specific activation of phospholipases, leading to the release of PUFAs and to their dispatching towards specific signalling pathways. Furthermore, it increasingly appears that oscillations of Ca^{2+} concentrations are crucial for the communication between glial cells and neurons and for

synchronising the physiological responses within the brain [15]. In return, do the PUFAs have an influence on the Ca^{2+} signalling in astrocytes? Sergeeva et al. [16] review and address this fascinating question by measuring the agonist-induced Ca^{2+} signals (influx, release and store replenishment) in astrocytes beforehand incubated with AA, EPA or DHA. The very comprehensive model of the authors reveals that PUFAs modulate the steady state level of internal Ca^{2+} and hence the ability of astrocytes to respond to further activation by external stimuli. The conclusion of this study is that the "insensibilisation" brought about by free PUFAs may protect the surrounding cells from pathological overstimulation, offering a relevant and remarkable explanation of the neuroprotective mechanisms of AA and DHA.

However, PUFAs also present a dark side, including their high sensitivity to oxidative reactions which may be generated in neuropathological conditions, and which may produce adverse effects in the brain. Models of oxidative injury are needed to identify the cellular targets of reactive oxygen species (ROS) within brain regions. Since chronic iron accumulation is thought to be associated with oxidative stress in several neurodegenerative diseases, Ong et al. [17] studied the generation of toxic aldehyde compounds that are produced from the release and peroxidation of PUFAs in response to intracerebroventricular injection of ferrous ammonium citrate. They observed by microscopy the iron-induced immunolabelling of hydroxynonenal (HNE) and of cytosolic phospholipase A_2 (cPLA $_2$) in the pyramidal neurons of the rat hippocampus. HNE positive cells exhibited features of injured neurons, showing that this model mimics situations where there is increased brain oxidative stress due to iron accumulation *in vivo*. Furthermore, the data give information on the transient induction of cPLA $_2$ and on the anti-peroxidative mechanisms that are able to clear the HNE immunoreactivity within weeks post-injection. One interesting conclusion of

Ong et al. is that rat neurons have a remarkable ability to tolerate and recover from a single episode of severe oxidative stress.

The impact of dietary PUFAs, especially of AA and DHA, on the neurodevelopmental outcomes in neonates receiving breast milk or milk replacers is still a controversial question. Although breast milk feeding is considered as being the "golden standard", human milk is submitted to high variability regarding the concentrations of AA and DHA among populations and among individuals from the same population [18]. Feeding with milk replacers however raises the question of supplementing with DHA alone, or with AA and DHA, and if so in which ratio. In any case, the effects, beneficial or not, on the development of mental and visual functions need to be evaluated. The study by Lauritzen et al. [19] examined if an increased content of DHA in the milk of Danish mothers with a habitual fish intake below the Denmark population median and receiving a fish oil-supplementation, may affect the mental development of the infants as compared to a control group receiving olive oil-supplementation and to a reference group with median fish intake. In particular, the authors evaluated the outcomes on problem solving at nine months of age and early language acquisition. The data indicate that fish oil-supplementation of the lactating mothers may have a slightly positive effect on the problem solving ability of the infants, but only in girls. However, maternal fish oil-supplementation also resulted in a transient reduction in vocabulary comprehension at one year of age, especially in boys, and word production at one year was inversely associated with DHA levels in infant erythrocytes. Therefore, the study by Lauritzen et al. shows that increasing the DHA-content of breast-milk may affect the early language acquisition of breast-fed infants. Although DHA-related long-term adverse effects have not been observed until now, the observations of Lauritzen et al. highlight that it is necessary to optimise the dietary supplies in PUFAs of lactating mothers,

especially with regards to the relative concentrations of long-chain PUFAs from both the n-6 and n-3 series.

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