LETTER TO THE EDITOR

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The Unsaturated Brain: An Evolutionary Compromise?

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To the Editor: The brain has a high content of polyunsaturated fatty acids (PUFAs), which are critical for neurodevelopment, neurotransmission, rapid metabolic turnover and repair [Davletov and Montecucco, 2010]. The high susceptibility of PUFAs to peroxidation mediated by reactive oxygen species (ROS), however, results in an increased vulnerability of the brain to oxidative damage [Barja, 2004]. The production of ROS by mitochondria (e.g. electron transport chain; alpha-ketoglutarate dehydrogenase in the Krebs cycle), peroxisomes or microglia is further exacerbated by the high oxygen consumption of brain [Barja, 2004; Adam-Vizi, 2005]. Moreover, the oxidative challenge for brain is worsen by the relative paucity of antioxidant enzymes compared with other organs. Considering the prominent role of neuronal signalling pathways as regulators of organismal response to environmental stimuli, PUFAs may increase the oxidative stress threat for this system, hence jeopardizing its normal function.

The continuous degradation and synthesis of RNAs is responsible of the metabolic changes essential for cell survival, but also of the rapid organismal adaptation to new environmental conditions. Oxidative damage to both coding- and non-coding RNAs and their degradation control system may therefore affect the regulation of gene expression and, potentially, result in protein synthesis failure. In turn, this failure may impair the organismal capacity of flexibly adapting to a novel or unusual input from the internal or external environment [Nunomura et al., 2009; He, 2010]. An important consequence of this impairment is the development of neurodegenerative disorders. Accumulating evidence suggests that oxidative RNA damage may actively be involved in the pathomechanisms of neurodegeneration [Nunomura et al., 2009]. Because of its biochemical structure, RNAs may be more susceptible to oxidative insults than DNA [Nunomura et al., 1999]. RNAs may also be an important target of oxidation because they are relatively abundant in the cell and they are mostly located in the vicinity of mitochondria, which are the primary source of ROS [Nunomura et al., 1999]. As a consequence, oxidative damage to RNA rather than DNA may be a more proximate cause of impairment in neuronal functioning through the alteration of brain gene expression machinery. Specific protective mechanisms of RNAs and their degradation control would be therefore expected to occur in neurons [Houseley and Tollervey, 2009]. May the high susceptibility of PUFAs to peroxidation indirectly play a role in the defence system of RNAs and, therefore, of the gene expression regulatory system in the nervous system? Although the functions of PUFAs in the nervous system are still far from being fully understood, recent studies have shown that PUFAs may affect the expression of many genes and that these effects appear to be independent of any changes in membrane composition [de Urquiza et al., 2000; Kitajka et al., 2002, 2004]. It is plausible to speculate that the high vulnerability to peroxidation of free PUFAs in neurons, coupled with their relative abundance in the brain, might play a passive protective role of RNAs, hence limiting their oxidation. Some support for this hypothesis comes from a recent study that has suggested a potential antioxidant role of PUFAs [Kim et al., 2010]. Notably, supplementation with omega-3 or omega-6 PUFAs of cultured neurons from mice lacking the gene encoding palmitoyl-protein thioesterase-1, which mimic infantile neuronal ceroid lipofuscinosis, reduced ROS levels that are normally very high in these cells [Kim et al., 2010]. Under this scenario, a second question arises. As PUFAs are major components of neural membrane phospholipids and have a critical role in brain signal transduction and neuroplasticity [Davletov and Montecucco, 2010], can PUFAs embedded in the cell membrane contribute to the protection of RNAs? We infer that they can limit the diffusion of ROS into the cell because of their proneness to be peroxidized. This mechanism would limit the intercellular transmission of ROS and that the oxidative cascade will spread to RNAs. Peroxidation of PUFAs in the membrane phospholipids has, however, a number of negative downstream effects on the cell, such as the decrease in fluidity and increase in permeability. Consequently, it is of fundamental importance the existence of a turnover mechanism that compensates for oxidative PUFA damage. Many studies have provided a wealth of evidence that there may be at least two mechanisms regulating the

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turnover of PUFAs. First, peroxidized phospholipids can be repaired by the enzymes phospholipase A2 and acyl-transferase [Lauritzen et al., 2001]. Second, unesterified PUFAs present in plasma lipoproteins can be actively transferred to the nervous system and then incorporated into neuron membranes to replace PUFAs lost by metabolic reactions [Rapoport et al., 2001]. Regarding this second mechanism, specific models have demonstrated that the rates of incorporation of plasma unesterified PUFAs into neuron membranes in adult rats and humans are sufficiently high to compensate for metabolic losses of phospholipids [Rapoport et al., 2001]. It is also important to stress here that there is large variation among animal species in brain development and relative concentrations of neural fatty acids [Kreps et al., 1963]. To this end, studies carried out on a larger diversity of species, as well as over differing time frames in the life cycle would be required to analyze inter-species differences and potential dynamic changes over consecutive life-history stages, which may be dependent on the alterations in the ratio and brain distribution of PUFAs.

In view of these considerations, how can we reconcile in evolutionary terms the number of functions that PUFAs have in the brain? We propose here an integrative model where natural selection has operated in order to optimize a molecular compromise among the costs and benefits of having a brain rich in PUFAs, and the interaction of PUFAs themselves with other molecules involved in neuronal development, gene expression (e.g. interactions with ligands that bind to response factors) and oxidative metabolism (e.g. enzymes that remove or repair lipid peroxidation compounds). It is implicit in our statement that the multiple pathways involved in neuronal signalling, RNA metabolism and intracellular redox regulation show a lower than expected optimal functionality because natural selection operated in order to optimize a balance among the different biochemical pathways rather than the functioning of a single trait at a time. Our proposal also implicates that the biochemical pathways would be functionally integrated, possibly resulting in an evolutionary module. We think that understanding the biological relevance of RNA protection by PUFAs and of its evolutionary underpinnings may explain fundamental aspects of selective pressures modulating brain evolution in vertebrates, and reveal important targets for neuromedicine approaches that seek to slow down the progression of neurodegenerative diseases.

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