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Fatty Acids and Autism Spectrum Disorders: The Rett Syndrome Conundrum

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ABSTRACT

Autism spectrum disorders (ASDs) are epidemically explosive clinical entities, but their pathogenesis is still unclear and a definitive cure does not yet exist. Rett syndrome (RTT) is a rare genetically determined cause of autism linked to mutations in the X-linked *MeCP*2 gene or, more rarely, in *CDKL*5 or *FOXG*1. A wide phenotypical heterogeneity is a known feature of the disease. Although several studies have focused on the molecular genetics and possible protein changes at different levels, to date very little attention has been paid to fatty acids in this disease, which could be considered as a natural paradigm for the ASDs. To this regard, a quite enigmatic feature of the disease is the evidence in the affected patients of an extensive peroxidation of polyunsaturated fatty acids (arachidonic acid, AA, docosaexahenoic acid, DHA, adrenic acid, AdA and, to a lesser extent, eicosapentaenoic acid, EPA), in contrast with amelioration of the redox changes and phenotypical severity following the supplementation of some of those same fatty acids (DHA + EPA). Therefore, fatty acids may represent a kind of *Janus Bifrons* in the particular context of RTT. Here, we propose a rational explanation for this apparent "fatty acid paradox" in RTT. A better understanding of this paradox could also be of help to get a better insight into the complex mechanism of action for polyunsaturated fatty acids in health and disease.

Keywords: Fatty Acids; Arachidonic Acid; Docosahexaenoic Acid; Adrenic Acid; Eicosapentaenoic Acid; Rett Syndrome; Autism Spectrum Disorders

1. Background

Polyunsaturated Fatty Acids (PUFAs) are becoming a hot topic in the research for neurodevelopmental and neuropsychiatric disorders [1-3]. Speaking about developmental disorders, such as Autism Spectrum Disorders (ASD) the current scientific thinking is mainly focused on genetic and/or neurologic approaches. However, for these conditions the cellular approach, which stresses what is ubiquitous and essential for cell function, seems far too often to be neglected. In this sense, PUFAs are really ubiquitous and essential components of cell membranes, where the majority of the cell machinery for intra- and inter-cellular communications (*i.e.*, involving signalling and transduction) resides and controls the intracellular environment integrity. In particular, within the nervous tissue, PUFAs influence neurogenesis and neurotransmission as their metabolites modulate immune and inflammatory processes, as well as oxidative stress (OS).

2. Rett Syndrome: A Unique Natural Model of Neuroregressive Disorders

In recent years, our group has deeply explored the link between PUFAs and Rett syndrome (RTT), an X-linked dominant neurodevelopmental disorder that predominantly affects females with an incidence of one in 10,000 - 15,000 female births [4,5]. Affected patients manifest

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various neuro-psychiatric features, including autistic traits, epileptic seizures, gait ataxia, stereotypies and loss of finalistic hands use [4]. Mutation of the *MECP*2 gene accounts for approximately 90% of cases with classic RTT [6]. Besides the classic or typical presentation, atypical RTT phenotypes have been identified, including the "so-called" preserved speech variant (usually associated with *MECP*2 mutations), early seizure (often related to *cyclin-dependent kinase-like* 5, *CDKL*5, gene mutations) and the congenital variant (often linked to *Forkhead box G*1, *FOXG*1, gene mutations) [7].

To date, the biological mechanisms linking the gene mutation to the phenotypic expression of the disease, including its wide heterogeneity, are yet to be clarified. However, recent discoveries, mainly by our team, concerning the emerging role of alteration of the redox homeostasis offer an alternative explanation which is not mutually exclusive with others previously proposed.

From our perspective, RTT represents a unique model of chronic oxidative stress with autistic features that are clearly linked to a gene mutation in which *de novo* sporadic mutations of the *MECP*2 accounts for the great majority of the causes. Nevertheless RTT also represents a complex and fascinating field of research as cumulating evidence points out that it is not a simple monogenic disease [8] as epigenetic mechanisms clearly play a role [9]. A valuable feature of the disease is the availability of several different experimental models, where the spearhead is represented by the reversibility models [10,11] that offers a unique resource for testing possible cause-effect relationships for several neuro-regressive human disorders, also of higher social impact.

3. Lipid Metabolism in RTT

Several lipid abnormalities in brain tissue and blood are reported in RTT. Altered lipid and ganglioside patterns in cerebrum, cerebellum, and cerebrospinal fluid of patients have been described [12-14]. Some of these brain lipid changes are associated with neuropathological alterations, including loss of Purkinje cells, atrophy, synaptic and myelin abnormalities in frontal cortex [12-15]. Decreased serum levels of very long-chain fatty acids (VLCFA) and carnitine have also been evidenced in RTT patients [16,17]. It can be speculated that low carnitine levels impede transportation to mitochondria, thus inhibiting the oxidation of long-, medium- and short-chain fatty acids, which is to a certain extent compensated by intensified β-oxidation of VLCFA in the peroxisomal system [16].

Interestingly, circulating levels of two adipocytokines (leptin and adiponectin) are also found to be increased in RTT patients, as compared to those of healthy controls [18,19]. Growth failure is a common feature of RTT patients and many individuals show clinical signs of moderate to severe malnutrition [20]. Moreover, increased plasma levels of leptin are detectable in RTT patients, but they are unrelated to the body mass index, thus suggesting that leptin might participate to clinical manifestations of the disease other than weight balance and adiposity [18]. Indeed, both adipocytokines could act, in either synergic or antagonistic ways, in several metabolic and immunological processes [21].

More recently, our group has shown that RTT patients have an altered plasma lipid profile with high levels of high density lipoproteins (HDL) and low density lipoproteins (LDL), as a possible consequence of an oxidative posttranslational mechanism in the Scavenger Receptor B1(SRB1) which mediates the selective uptake of cholesteryl esters from HDL as well as LDL into the cells without internalizing lipoprotein particles [20]. In particular, decreased SRB1 levels in RTT skin fibroblasts cultures have been demonstrated to be the consequence of its binding with 4-hydroxy-2-nonenal (4HNE), a product of lipid peroxidation, and of its increased ubiquitination [22]. Therefore, the link between lipids and OS in RTT appears to be far more complex than previously thought.

4. The "Fatty Acids Paradox" in RTT

Biochemical evidence of an extensive PUFAs peroxidation (arachidonic acid, AA, docosahexaenoic acid, DHA, adrenic acid, AdA and, to a lesser extent, eicosapentaenoic acid, EPA) is present in the affected patients. Indeed, abnormal plasma levels of lipid peroxidation end-products [F_2-isoprostanes (F_2-IsoPs), F_4-neuroprostanes (F_4-NeuroPs), and F_2-dihomo-isoprostanes (F_2-dihomo-IsoPs)] have been detected in RTT, whose precursor fatty acids are AA, DHA and AdA, respectively [8,23-29].

A quite enigmatic feature of the disease is that exogenous administration of ω-3 PUFAs (DHA + EPA), at disease stages I-IV, has been shown to moderately reduce clinical severity and significantly reduce the levels of IsoPs and 4-HNE PAs in RTT patients [30]. Thus, contrary to expectations, the assumed fatty acids are not further oxidized, while the actual endogenous IsoPs production is reduced (the "fatty acid paradox") together with amelioration of the clinical disease severity.

Conceivably, an excess of peroxidation end products from ω-6 and ω-3 PUFAs would actually imply an excessive consumption of these PUFAs in the cell membranes, thus paving the way for a new perspective on the nutritional horizons in RTT.

This observation generates an interesting concept according to which the increased isoprostanes levels in RTT are not simply the effect of the peroxidation of the

PUFA precursors following the attack by radical oxygen species (ROS), but rather the effect of a potential dysregulation of the molecular targets of ω-3 PUFAs, including ionic channels and/or eicosanoids biosynthesis. In addition, it is still unclear whether the action of ω-3 PUFAs is a direct one or it is, more likely, mediated by secondary metabolites [31-33]. As RTT girls appear to chronically suffer from oxidation of PUFAs, either ω-3 (*i.e.*, DHA/EPA) or ω-6 (*i.e.*, AA, AdA), but, at the same time, benefit from ω-3 PUFAs supplementation, it can be inferred that these patients would need an ω-3 PUFAs replacement as a consequence of a persistent PUFAs oxidation within the chronic OS context. On the other hand, it is also possible that, in RTT, the endogenous PUFAs are, for their own nature, more susceptible to the OS as compared to the exogenous ones. Therefore, administered PUFAs may be seen as counteracting this intrinsic defect. Interestingly, impaired cholesterol metabolism has been very recently demonstrated in a *Mecp*2-null mouse model of RTT, with statin treatment leading to improvement of motor symptoms and conferring increased longevity [34]. This report appears to be in agreement with our prior observation regarding an unexplained hypercholesterolemia in RTT patients [22] and with our prior inferences on a possible use of statins in RTT as derived by comparison of full exome sequences in two special pairs of RTT sisters harbouring the same *MeCP*2 mutation and discordant clinical phenotype [8]. Notably, ω-3 PUFAs have been widely used, either alone or in combination with pharmacological molecules, as lipid lowering agents in hypercholesterolemia, with consistently fewer side effects as compared to those reported for statins [35]

Overall, the lipid metabolism in RTT appears to be a surprisingly fruitful field of research to be explored in the coming years.

5. Conclusion

Surprisingly, the use of exogenous fatty acids (ω-3 PUFAs), as dietary supplementation, and the concomitant identification of their peroxidation end-products have unveiled a previously unrecognized feature of RTT, which we would like to define as the "fatty acid paradox" of the disease. Our interpretation, at this time, is that these fatty acids may represent a molecular target for the disease, so far thought to be simply a primary genetically determined developmental disorder of the brain. Rather, RTT should be perhaps considered as a developmental brain disease consequent to a complex lipid metabolism disorder in a pro-oxidant shifted redox imbalance context.

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