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REVIEW OPEN ACCESS

Idiopathic focal epilepsy in children and adolescents: roles of perinatal pain, amyloid-β oligomers and DHA (omega-3 fatty acid) deficiency☆

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Abstract – In children and adolescents, epilepsy is a chronic disease characterized by the paroxysmal onset of seizures resulting from abnormal cellular excitability. Idiopathic epilepsy is a disease of apparent spontaneous origin whose cause or mechanism is unknown. This opinion review describes the pathogenetic mechanisms behind epilepsy, as well as its generating and aggravating factors. A triggering factor is perinatal pain that generates amyloid-β (Aβ) oligomers that is not completely eliminated. An aggravating factor is a deficiency of DHA — due to diet or specific *FADS2* alleles (Δ6-desaturase gene) — which is a preferential ligand of the PPARα-RXRα and PPARɣ-RXRα heterodimers. These two factors have impacts on the glutamatergic pathways: (i) metabolic homeostasis as a function of stimulation (regional blood flow); (ii) flow rate of GLUT-1 transporters (glucose, ascorbic acid precursor); (iii) regulation of oxidative stress; (iv) repair of oxidative injuries; (v) priority given to the non-amyloidogenic pathway; (vi) proteolysis of Aβ residues and their removal. The originality of this approach resides in particular in highlighting the fundamental role played by DHA. Understanding the risk factors can help prevent epilepsy onset, decrease epilepsy prevalence in children and adolescents and aid healthcare professionals in identifying high-risk populations and making plausible preventive nutritional measures based on DHA supplementation very early.

Keywords: Epilepsy / perinatal pain / amyloid β / DHA depletion / PPAR-RXR / mechanisms

Résumé – Épilepsie focale idiopathique chez les enfants et les adolescents : rôles de la souffrance périnatale, des oligomères amyloïdiques β et de la carence en DHA (acide gras oméga-3). Chez les enfants et les adolescents, l'épilepsie est une maladie chronique caractérisée par l'apparition paroxystique de crises résultant d'une excitabilité neuronale anormale. Une épilepsie idiopathique est une maladie dont la cause ou le mécanisme est inconnu et dont l'origine est apparemment spontanée. Cette revue d'opinion décrit les mécanismes pathogéniques, ainsi que les facteurs générateurs et aggravants. Un facteur déclenchant est une souffrance périnatale qui génère des oligomères peptidiques amyloïdes-β (Aβ) qui ne sont pas éliminés. Un facteur aggravant est la carence en DHA (alimentation, allèles spécifiques *FADS2* – gène de la Δ6-désaturase) en tant que ligand préférentiel des hétérodimères PPARα-RXRα et PPARɣ-RXRα. Ces deux facteurs ont des répercussions sur les voies glutamatergiques : (i) homéostasie métabolique en fonction de la stimulation (débit sanguin régional); (ii) débit des transporteurs GLUT-1 (glucose, précurseur de l'acide ascorbique); (iii) réparation des lésions oxydatives; (iv) priorité donnée à la voie non amyloïdogène; (v) protéolyse des résidus Aβ et leur élimination. L'originalité de cette approche réside notamment dans la mise en évidence du rôle fondamental joué par le DHA. La compréhension des facteurs de risque peut permettre de prévenir l'apparition de l'épilepsie, de diminuer sa prévalence chez l'enfant et l'adolescent, ainsi qu'à aider les professionnels de santé à identifier les populations à risque et à mettre en place des mesures nutritionnelles préventives plausibles basées sur une supplémentation en DHA très précoce.

Mots clés : Épilepsie / souffrance périnatale / amyloïdes β / Déficience en DHA / PPAR-RXR / mécanismes

☆ Contribution to the Topical Issue: "Lipids and health / Lipides et santé".

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Highlights

- A triggering factor is a perinatal pain that generates amyloid-β peptide oligomers (Aβ) that are not completely eliminated.
- Depletion DHA is an aggravating factor (diet, specific *FADS2* alleles-Δ6-desaturase gene).
- These two factors have impacts on the glutamatergic pathways.
- DHA acts as a preferential ligand of the PPARα-RXRα and PPARɣ-RXRα heterodimers.

1 Introduction

In children and adolescents, epilepsy is a neurological disease that affects the functioning of the central nervous system. This chronic disease is characterized by the paroxysmal onset of seizures, which vary in nature depending on the patient. An epileptic seizure occurs due to abnormally prolonged electrical activity in a group of neurons in the cerebral cortex. In the case of an epileptic seizure, neurons become hyperexcitable, *i.e.*, a single stimulation leads not to an action potential but to a repeated series of action potentials with no rest period. During seizures, hyperexcitability is frequently associated with hypersynchrony, with several groups of neurons generating trains of action potential at the same time and at the same rhythm, amplifying the intensity of symptoms. Epilepsy can take a variety of forms. In children and adults alike, a distinction is made between partial and generalized forms. These two forms of epilepsy are further divided into so-called idiopathic forms, where the cause is not identified, and so-called structural forms, which are visible upon examination (scanner, MRI). When a child suffers from partial or focal epilepsy, this is sometimes described as benign idiopathic epilepsy, characterized by the absence of prior or progressive brain lesions. The most common forms of epilepsy in children are rolandic paroxysmal epilepsy (benign partial epilepsy of childhood with centrotemporal spikes) and early-onset benign occipital epilepsy, which first manifests between the ages of 3 and 13 years. Focal epilepsies, which account for approximately 60% of all forms of epilepsy, begin at a specific point in a region of the brain (epileptogenic focus) and can eventually spread to other regions. Focal epilepsies are typically associated with abnormal electroencephalogram activity in one hemisphere of the brain. They warrant treatment if they are too frequent, if they occur during the day, or if they disrupt the child's daily life. Other partial epilepsies in children, known as structural epilepsies, can be linked to abnormal electrical activity in a particular region of the brain. Genetic mutations in the voltage-gated sodium channels *SCN 1 A* and *SCN 2 A* are responsible for rare epilepsies (Bergren *et al.*, 2005), which require treatment. Epileptic seizures occur when neurons in the brain become excessively active. When this activity reaches a certain level, the seizure is triggered (epileptogenic threshold). For seizure symptoms to appear, a large number of brain neurons must malfunction simultaneously. Their location depends on the type of epilepsy. The clinical signs of a seizure can vary depending on the location of the epileptic focus and the number of neurons involved. Symptoms may include psychic symptoms (such as anxiety and fear), vegetative symptoms (such as palpitations, hot flushes, shivering, or sweating), sensory symptoms (such as tingling in an arm or leg), and motor symptoms (such as jerky contractions in an arm or leg). The International League Against Epilepsy (ILAE) has a revised operational classification of seizure types (Fisher *et al.*, 2017). Treatment of these illnesses is most often based on the use of anti-epileptic drugs, which prevent the recurrence of seizures, and not on the epileptogenic mechanisms (Perucca *et al.*, 2018); they do not cure the illness itself as they do not treat the cause (French *et al.*, 2004). Most anti-epileptic drugs act by lowering neuronal excitability through their action on pre- and/or postsynaptic transmembrane channels (sodium, calcium, chlorine) (Landmark, 2007). Some epilepsies are drug-resistant.

In 1862, William Little speculated that the origin of idiopathic epilepsy in children was perinatal pain from asphyxia (Nielsen and Courville, 1951). Epileptic seizures connected to perinatal hypoxia may occur in early childhood or later on (Watanabe *et al.*, 1980; Bergamasco *et al.*, 1984). More rarely, certain idiopathic epilepsies are linked to mutations in ion channel genes, located on the neuron's membrane and enabling ion exchange and thus depolarization and repolarization. Moreover, the EFSA's (European Food Safety Authority) Panel on Nutrition, Novel Foods and Food Allergens (NDA) has noted that docosahexaenoic acid (DHA) has a well-established role in brain function. The Panel concluded there is a relationship of cause and effect between the consumption of DHA and the maintenance of normal brain function (EFSA, 2010). It has been reported that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are polyunsaturated fatty acids (PUFAs), have anticonvulsant effects. However, the mechanism of EPA and DHA on epilepsy is still unclear.

As well as a review of the literature, in this article we present several original concepts and hypotheses related to idiopathic focal epilepsy in children and adolescents. We assume that this form of epilepsy is the result of a combination of two essential factors, whose mechanisms we will present in detail. Firstly, a triggering factor: perinatal pain generating amyloid-β peptide oligomers (Aβ) that are not reduced. They are the corollaries of pain. The first description of Aβ came from the neurological examination of an epilepsy patient by Blocq and Marinesco more than a century ago, and it suggests a strong link between epilepsy and Alzheimer's disease (Buda *et al.*, 2009). Secondly, an aggravating factor: DHA deficiency (genetic, diet). These factors are interdependent. The originality of this approach resides in particular in highlighting the fundamental role played by DHA, whether it be synthesized by the Δ6-desaturase enzyme or provided by the diet. Major facilitator superfamily domain-containing protein 2 (Mfsda), expressed exclusively in endothelium of the blood brain barrier of micro-vessels, is the major transporter for DHA uptake into brain (Nguyen *et al.*, 2014). Understanding the risk factors can help prevent the onset of epilepsy, decrease the prevalence of epilepsy and its associated comorbidities in children and adolescents, and aid healthcare professionals in identifying high-risk populations and developing plausible prevention strategies. Therefore, it is necessary

to identify individuals who would be most likely to benefit from preventive nutritional measures.

2 Perinatal pain and amyloid-β peptide oligomers

Hypoxic-ischemic encephalopathy is the most frequent type of perinatal pathology that predisposes to epilepsy. It is caused by a lack of oxygen to the brain before or shortly after birth. The causes of perinatal hypoxia include low oxygen levels in the mother's bloodstream before or during birth, issues with theplacenta such as separating from the womb too early, issues with the umbilical cord during delivery, prolonged or difficult delivery, maternal hypertension or hypotension, and airway obstruction at birth (Bergamasco *et al.*, 1984; Senanayake and Roman, 1993; Ketata *et al.*, 2024). As cells undergo hypoxia, ATP production is reduced due to reduced mitochondrial metabolism. Hypoxia then presents a "non-ideal state" in which passive distribution of ATP is insufficient to provide subcellular components with the energy required for their respective processes (Flood *et al.*, 2023). Hypoxia diminishes ATP utilization by downregulating protein translation and the activity of the Na^+/K^+-ATPase (Wheaton and Chandel, 2011).

In addition to oxygen deficiency, umbilical cord compression can also restrict regional cerebral blood flow, thereby affecting the supply of essential metabolic nutrients (glucose, dehydroascorbic acid, DHA, EPA, testosterone, estradiol, IGF-1, etc.) and limiting their availability to astrocytes, neurons, and microglia. The critical importance of regional cerebral blood flow control was reported as early as 1890 in a landmark publication (Roy and Sherrington, 1890). These nutrients maintain the optimal balance between energy homeostasis and antioxidant protection. An imbalance in these nutrients can result in energy depletion, oxidative stress, and inflammation, ultimately causing cell death, which can contribute to the development of cerebral palsy and epileptogenic lesions. A deficiency in energy supply, associated with oxidative stress and neuroinflammation, is a trigger and driving force in acquired epileptogenesis (Samokhna *et al.*, 2017; Zylberter and Zylberter, 2017). Decreased glucose utilization during quiescent (interictal) periods is a widely recognized biomarker for human epilepsy (Pittau *et al.*, 2014). Hypometabolism, indicated by reduced glucose consumption, is a very early sign of epileptogenesis (Bascunana *et al.*, 2016; Zhang *et al.*, 2015). This phenomenon is further supported by findings on GLUT-1 deficiency syndrome, a genetic disorder first described in 1991 as a developmental encephalopathy characterized by infantile-onset refractory epilepsy (Pearson *et al.*, 2013).

DHA depletion in newborns exacerbates this condition. During the perinatal phase, DHA depletion results from maternal DHA dyslipidemia (from the umbilical vein or breast milk). DHA plays a major role in the up-regulation of regional cerebral glucose flow. For example, in elderly monkeys, the supply of DHA significantly increases in regional cerebral blood flow in response to stimulation (Tsukada *et al.*, 2000). In humans, higher erythrocyte EPA/DHA levels are related to higher regional cerebral blood flow in the brain (Amen *et al.*, 2017). In a recent article, we described the mechanisms of glucose and ascorbic acid uptake into astrocytes' intracellular space, as well as the different stages of its transport and transformation into ATP (lactate shuttle, etc.) (Majou and Dermenghem, 2023). The first way the body meets urgent demand is to increase the blood flow through vasodilatory responses generated by nitric oxide (NO) (Moncada *et al.*, 1991). NO is produced by both eNOS and nNOS (nitric oxide synthase) (Reis *et al.*, 2017) (see below). If production is insufficient, the second mechanism for NO production is to increase GLUT-1 density through the translocation of this transporter from a reservoir of cytoplasmic vesicles. After the phosphorylation of AS160 (Akt substrate of 160 kDa), a Rab GTPase-activating protein located on the membranes of these intracellular vesicles (Treebak *et al.*, 2006), GLUT-1 translocates to and crosses the blood brain barrier (Andrisse *et al.*, 2013). Phosphorylation of AS 160 depends on both ATP and the astrocytes' intracellular Ca^{2+} levels in. The integration of the three means of phosphorylation (PI3K/Akt pathway, AMPK:AMP-activated protein kinase and calmodulin/CaMKKβ) enables the reaction. The third pathway is to increase GLUT-1 synthesis by stimulating *SLC2A1* (GLUT-1 gene) transcription. The *SLC2A1* gene is an estrogen-regulated gene with transcription regulation by estrogen receptors (Wang *et al.*, 2004), which are also present in astrocyte membranes. A tandem of two key molecules, free estradiol and DHA, is involved in this critical regulation. Their relationship is synergistic and reciprocal: free estradiol with genomic and non-genomic actions *via* ERα, and DHA *via* the PPARα-RXRα and PPARɣ-RXRα heterodimers (Majou and Dermenghem, 2023). GLUT-1 deficiency is associated with idiopathic epilepsies (Arsov *et al.*, 2012; Janigro, 1999).

We can assume that the chronic oxidative stress induced by perinatal pain, aggravated by DHA depletion, causes cryptic lesions in a set of neurons and/or astrocytes, probably in the hippocampus, in regions characterized by resting membrane potential, which are not a priority in cerebral blood flow. These cryptic lesions are not visible on medical imaging, are asymptomatic, with no cellular destruction and no apparent traumatic manifestations. The newborn may be slightly hypothermic but still have an Apgar of above 7. The amyloid precursor protein (APP), and its derivative sAPPα (soluble amyloid precursor protein α) generated by α-secretase cleavage, play an important role in neuronal growth and synaptic plasticity. Their increased expression in all kinds of cases of neuronal injury represents an acute phase response in the region surrounding the injury where it is localized (Van den Heuvel *et al.*, 1999) in particular in the neonatal brain following hypoxic-ischemic injury (Baiden-Amissah *et al.*, 1998). Elevated glutamate concentration activates the NF-kappaB transcription factor binding site from the regulatory region of *APP* gene (Grilli *et al.*, 1996), by a pathway requiring the Ca^{2+}/calmodulin-dependent kinase (CaMKII) (Meffert *et al.*, 2003). sAPPα demonstrates neuroprotective and neurotrophic functions (Corrigan *et al.*, 2014; Plummer *et al.*, 2016). It reduces neuronal cell loss and axonal injury (Thornton *et al.*, 2006) and restores synaptic plasticity and partially restores spine density deficits (Fol *et al.*, 2016). We

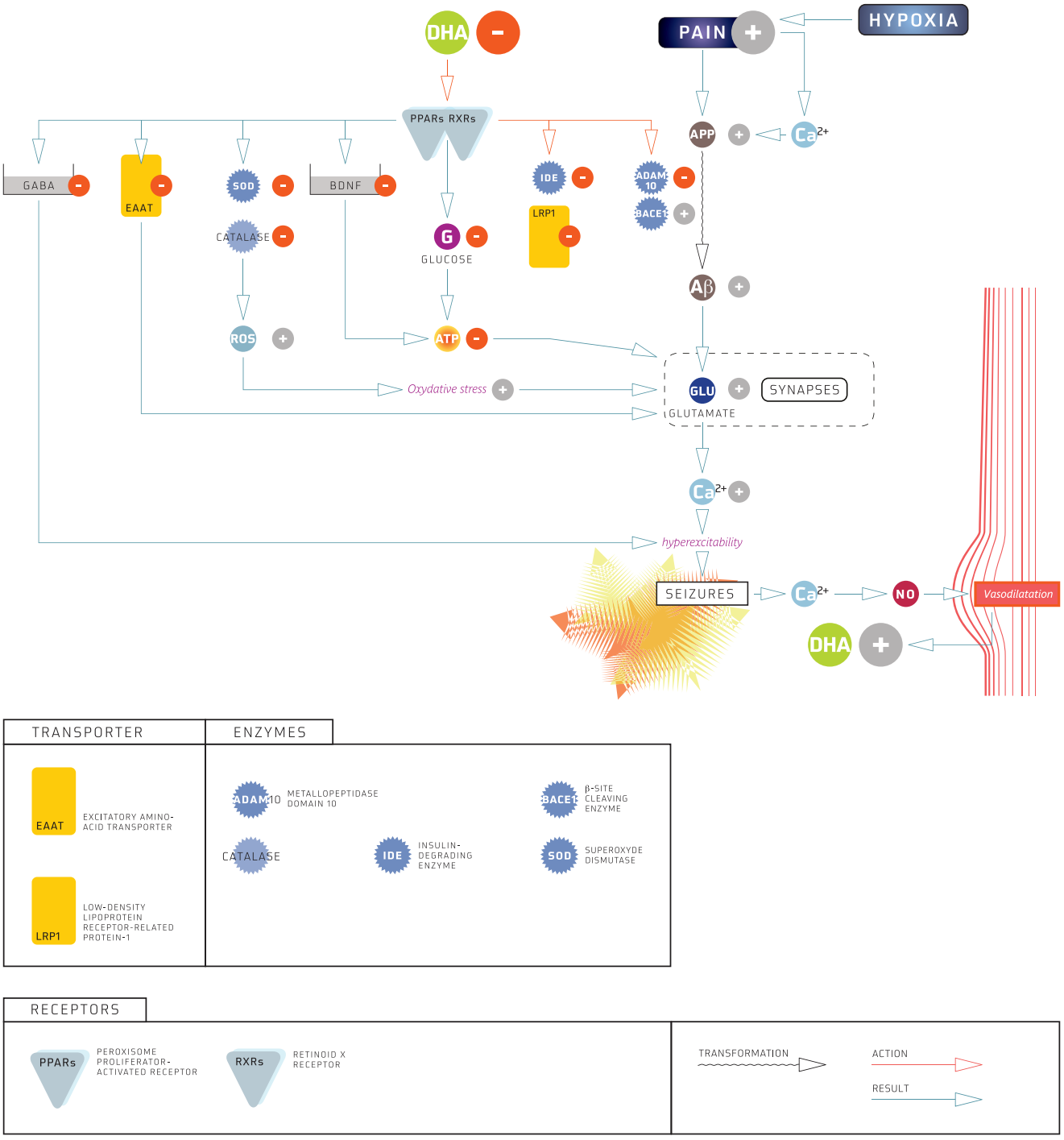

Fig. 1. The origins of epileptic seizures.

assume that these cryptic lesions are at the origin of cerebral amyloidosis (Costa *et al.*, 2016; Joutsa *et al.*, 2025; Minkeviciene *et al.*, 2009; Paudel *et al.*, 2020; Romoli *et al.*, 2021; Sheng *et al.*, 1994; Sima *et al.*, 2014). In a recent paper (Majou and Dermenghem, 2024a), we described how cerebral amyloidosis is the result of dynamic, APP-dependent regulatory mechanisms that reflect molecular competition and equilibria, and the chronicity nature of the phenomenon. In short, these mechanisms concern the synthesis of Aβ peptides with competition between the non-amyloidogenic pathway and the amyloidogenic pathway (*i.e.*, a competition between the enzymes ADAM10 and BACE1 respectively), on the one hand – phosphorylated PPARα-RXRα heterodimer modulates the transcription of *ADAM10* gene; PPARγ-RXRα activation reduces BACE1 mRNA levels – and the different processes of soluble Aβ

residue clearance, on the other hand. This clearance mobilizes both peptidases (NEP, and IDE) and removal transporters (LRP1, ABCB1, and RAGE) across the blood brain barrier ((Majou and Dermenghem, 2024b). The perinatal hypoxia leads to reduced NEP protein and activity levels in the cortex (Dubrovskaia *et al.*, 2009; Nalivaeva *et al.*, 2003) (Fig. 1). The accumulation of Aβ peptides and their deposition in the brain parenchyma arise from various reactional imbalances. It is important to note that the same is true for epilepsy of accidental origin (stroke). Cerebral ischemic injury leads to neurotoxic Aβ accumulation in the brain (Kang *et al.*, 2023; Ouyang *et al.*, 2021).

The description of the mechanisms set out above also reveals the two key molecules: (i) free estradiol, which has genomic and non-genomic action, and (ii) free DHA as the preferential ligand of PPARα-RXRα and PPARγ-RXRα heterodimers. DHA significantly increases non-amyloidogenic processing of APP, leading to enhanced secretion of sAPPα (Sahlin *et al.*, 2007; Eckert *et al.*, 2011; Yang *et al.*, 2011; Grimm *et al.*, 2016). Free estradiol and DHA are involved in Aβ peptide clearance; this concerns proteolysis by endopeptidases, and interaction with ApoE-Aβ, which are transporters of Aβ. When a certain level of chronic DHA deficiency is reached, the synthesis and persistence of Aβ occur at synapses. Confirming the role of soluble Aβ in idiopathic epilepsy, Zhu *et al.* (2018) showed that ADAM 10 suppresses epilepsy. Moreover, as in Alzheimer patients, the three ApoE isoforms (E2, E3, E4) bind directly to Aβ peptides both *in vitro* and *in vivo*. ApoE3 has greater affinity than ApoE4 for both Aβ40 and Aβ42 (Majou and Dermenghem, 2024). Native ApoE3's affinity for Aβ peptides is 2-3 times higher than that of ApoE4. More generally, ApoE forms complexes with Aβ, with ApoE2 and ApoE3 binding Aβ more efficiently than ApoE4 in epileptic patients (Aboud *et al.*, 2013). The ApoE4 allele is a possible risk factor for epilepsy (Joutsa *et al.*, 2017; Li *et al.*, 2016).

3 Active neurons and epileptic seizures

We can assume that as long as the neurons are at rest, Aβ concentrations do not increase. When DHA levels are normal, the clearance of Aβ amyloids occurs progressively over time until they are completely eliminated through the aforementioned pathway. During the first two years of human life, DHA is of vital importance. DHA rapidly accumulates in brain tissue as early as the third trimester of pregnancy. During this period, levels of the precursors linoleic acid (omega-6) and alpha-linolenic acid (omega-3) remain consistently low in the brain, while there is substantial accretion of long-chain desaturation products, arachidonic acid (ARA) (omega-6) and DHA (omega-3). At birth, DHA accounts for around 9% of total cortical fatty acid composition (Clandinin *et al.*, 1980), but DHA deficiency slows or prevents soluble Aβ clearance.

The human brain begins to form during pregnancy, but most neurons are not connected to each other when a child is born. Neurons connect and strengthen in response to the stimuli the baby receives from its environment. These connections between neurons are essential for the brain to function. Gray matter volume — which reflects the size and number of branches of brain cells — increases during childhood, peaking at different times depending on the region of the brain. This pattern of childhood peaks occurs not only with gray matter volume but also with the number of synapses and the density of neurotransmitter receptors. Axons, dendrites and synapses are produced in excess in humans until approximately 2 years of age; this phenomenon is known as "developmental exuberance" (Innocenti and Price, 2005). Synapses are then partially eliminated in a process of neural network optimization, retaining only mature, operational connections. This synaptic pruning continues until late adolescence (Jiang and Nardelli, 2016). This phenomenon is accompanied by axonal pruning involving mechanisms of axonal degeneration or retraction (Riccomagno and Kolodkin, 2015). Memory, for example, is shaped by the brain's evolutionary pathways, which, over time, give rise to sensory memory, followed by procedural memory, semantic memory, episodic memory, and working memory. In response to stimuli, neurons at rest are activated, triggering action potentials.

If activation involves a set of neurons that carry cryptic lesions induced by Aβs, they will have deleterious effects on synaptic connections. A chronic excess of soluble Aβ peptides increases the disruption of synaptic activity in down-regulating astrocytic glutamate (the most abundant excitatory neurotransmitter) uptake capacity in a concentration-dependent manner. This disturbance of glutamatergic synaptic transmission by soluble Aβs of neuronal origin, mainly dimers (Shankar *et al.*, 2008), switches the physiological state of a neuron to a pathological state with a further increase in the intracellular concentration of Ca^{2+}, induced particularly by the NMDA receptor and continuous membrane depolarization. These Aβ peptides alter synaptic transmission and cellular excitability by altering the function of voltage-gated calcium channels (Price *et al.*, 1998; Ramsden *et al.*, 2002), certain types of potassium channels (Colom *et al.*, 1998; Yu *et al.*, 1998), AMPA receptors (Chang *et al.*, 2006), NMDA receptors (Snyder *et al.*, 2005), and the α7 nicotinic receptor (Wang *et al.*, 2000; Dineley *et al.*, 2001), or by the formation of calcium-permeable membrane pores or channels (Arispe *et al.*, 1993; Bhatia *et al.*, 2000; Kawahara *et al.*, 2000; Kourie *et al.*, 2001; Kayed *et al.*, 2004; Demuro *et al.*, 2005). Aβ peptides form morphologically compatible ion-channel-like structures and elicit single ion-channel currents. These ion channels seem to destabilize cellular ionic homeostasis, thereby inducing cell pathophysiology (Quist *et al.*, 2005). Moreover, lipid peroxidation is induced by Aβ peptides, *via* two reactive products in particular (4-HNE and 2-propenal/acrolein). DHA has been shown to suppress 4-HNE generation (Geng *et al.*, 2020) and to decrease glutamate uptake in astrocytes by affecting the activities of glutamate transporters GLT-1 and GLAST in mice (Harris *et al.*, 1996; Butterfield *et al.*, 2002; Matos *et al.*, 2008). This effect is also reflected in decreased expression of EAAT2 (the human equivalent of GLT-1) in postmortem Alzheimer's disease brain tissue (Scott *et al.*, 2011) as well as reduced EAAT1 (the human equivalent of GLAST) in the hippocampus (Jacob *et al.*, 2007). This reduction was specifically noted in the vicinity of senile plaques (Jacob *et al.*, 2007; Hefendehl *et al.*, 2016). Astrocytic excitatory amino acid transporters (EAATs) are responsible for the uptake of a large fraction of glutamate at the synapse and they control glutamate homeostasis. EAAT2, which is concentrated in perisynaptic astrocytes, performs 90% of glutamate uptake. EAATs play essential roles in the maintenance of normal excitatory synaptic transmission,

the protection of neurons from the excitotoxic action of excessive glutamate, and the regulation of glutamate-mediated neuroplasticity. Therefore, dysfunction of EAATs, located primarily on astrocytes, can cause abnormal excitatory synaptic transmission, neuronal excitotoxicity, and the exaggeration of neuroplasticity-based events. Excess glutamate not recovered in time works not only as a point-to-point transmitter but also through spill-over synaptic crosstalk between synapses in which summation of glutamate released from a neighboring synapse creates extrasynaptic signaling/volume transmission (Okubo *et al.*, 2010). It activates NMDA receptors, but not AMPA receptors, on a neighboring cell (Asztely *et al.*, 1997). EAAT dysfunction is implicated in a variety of neurodegenerative and neurological diseases, including amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease, ischemia, and epilepsy (Nakagawa and Kaneko, 2013). And finally, glutamine synthase, which is particularly vulnerable to oxidative modification, is also a target of Aβ-induced oxidative damage (Boyd-Kimball *et al.*, 2005; Huang *et al.*, 2016). The activation of PPARγ-RXRα upregulates EAAT2 expression (Hou *et al.*, 2020). PPARγ-RXRα agonists increase both mRNA and protein expression and glutamate uptake *via* PPAR response elements (PPREs) as promoter (Garcia-Bueno *et al.*, 2007; Romera *et al.*, 2007). An agonist of PPARγ, DHA is the key molecule in the induced regulation of EAATs (Takahashi *et al.*, 2023). Therefore, EAAT levels are lower in DHA-deficient subjects, with a direct impact on the rate of glutamate recovery.

This slowing of glutamate uptake in the synaptic cleft causes hyperstimulation of the postsynaptic neuron with an increase in intracellular Ca^{2+} and excessive activation of nNOS and eNOS, which induces oxidative stress *via* "Janus-faced molecule" nitric oxide (NO) and its main highly oxidizing metabolite, peroxynitrite, whose effects depend on their concentration and chronicity. This slowing of glutamate uptake, and the epileptogenic process, are also linked with the over-production of pro-inflammatory cytokines such as inflammatory mediator cyclooxygenase 2 (COX-2), interleukin 1β (IL-1β), tumor necrosis factor α (TNFα) (Valles *et al.*, 2010) and interleukin IL-6 (Li *et al.*, 2011). Animal studies have shown the neurotoxic and pro-convulsive effects of both IL-6 and TNF-α in the brain (Li *et al.*, 2011). These proinflammatory cytokines activate transcription of the *NOS2* gene, which produces more inducible nitric oxide synthase (iNOS), which catalyzes nitric oxide (Singh *et al.*, 1996; Stancill *et al.*, 2021). IL-1β has been shown to increase neuronal hyperexcitability by enhancing glutamate release by astrocytes and reducing its uptake (Meng et Yao, 2020), as well as by upregulating NMDA receptors, which increases intracellular Ca^{2+} influx (Postnikova *et al.*, 2017). Soluble Aβ peptides can already induce neuronal hyperactivity before plaque formation (Busche *et al.*, 2012; Xu *et al.*, 2015). This Aβ-induced neuronal hyperexcitability (Busche *et al.*, 2012) is believed to trigger epilepsy (Minkeviciene *et al.*, 2009). The Aβ concentrations will increase as local and proximal neuronal activity increases. The seizure threshold depends on the local Aβ concentration (triggering concentration), which determines the glutamate concentration at a synapse and neighboring synapses by overflow of Aβ and unrecovered glutamate. The massive influx of Ca^{2+} into neurons is the key mechanism underlying the neuronal hyperexcitability that precedes seizures (Cano *et al.*, 2021). In DHA-deficient subjects, the inhibitory activity of GABA (γ-aminobutyric acid) – the main inhibitory neurotransmitter in the cerebral cortex that is formed within GABAergic axon terminals and released into the synapse – is reduced. DHA has been reported to facilitate the binding of GABA systems and increase the rate of desensitization of $GABA_A$ receptors by modulating the elasticity of the lipid bilayer (Søgaard *et al.*, 2006; Zhou *et al.*, 2022). DHA has been shown to reduce network excitability within the recurrent CA3 circuitry of the mouse hippocampus (Taha *et al.*, 2013). The inhibitory effects of GABA counterbalance the excitatory effects of glutamate. An imbalance between synaptic excitation and inhibition between these two neurotransmitters is implicated in hyperexcitability and epilepsy (Perucca *et al.*, 2023).

Moreover, in DHA-deficient subjects, the deleterious effects of Aβs are accentuated by reduced or delayed supply of glucose – and therefore of energy (ATP) – and antioxidant defenses (ascorbate, reduced glutathione/GSH, NADPH through the pentose phosphate pathway, in particular) (Stincone *et al.*, 2015) due to reduced GLUT-1 expression (Majou and Dermenghem, 2023). Oxidative stress resulting from excessive free-radical release is likely implicated in the initiation and progression of epilepsy (Shin *et al.*, 2011). It is worth noting that antioxidant enzymes Cu/Zn-SOD and catalase, and glutathione peroxidase 3 gene promoters, contain peroxisome proliferator response element (PPRE), indicating that they are directly regulated by transcription factors PPARα-RXRα (Inoue *et al.*, 2001; Liu *et al.*, 2012), and PPARγ-RXRα (Araújo *et al.*, 2016; Chung *et al.*, 2009; Hwang *et al.*, 2005; Kim *et al.*, 2017; Okuno *et al.*, 2010). Free DHA being the main ligand of PPARα/γ and RXRα, this binding deficiency explains the lack of antioxidant defenses. The ATP deficiency slows glutamate recovery by the astrocyte and the glutamate-glutamine cycle (Majou and Dermenghem, 2023). Glutamate is converted into glutamine by glutamine synthetase and shuttled back to neurons for glutamate synthesis (Allaman *et al.*, 2011). The glutamate-glutamine shuttle consumes two ATP molecules: one molecule of ATP for astrocytes to capture glutamate through the action of the Na^+/K^+-ATPase (Magistretti *et al.*, 1997; Schurr *et al.*, 1998), and one molecule of ATP to convert the glutamate to glutamine by glutamine synthase (Smith *et al.*, 1991). So, dysregulation of glucose metabolism can impact glutamate synthesis in the glutamate/glutamine cycle (Knight *et al.*, 2014). Astrocytes use the electrochemical gradient of sodium to introduce the glutamate (Pellerin *et al.*, 2003). The rate and velocity of Na^+ and K^+ input and output between two action potentials at a chemical synapse is critical, as this factor drives the polarization and depolarization of membranes. The return to resting potential depends on the reaction rate of the Na^+/K^+-ATPase located in the astrocytic membrane. Its enzymatic activity expels three Na^+ ions and imports two K^+ ions using energy from the breakdown of ATP to ADP (Sontheimer *et al.*, 1994; Pellerin *et al.*, 1997). This enzyme helps maintain resting transmembrane potential. It plays a critical role in energy metabolism and ion fluxes against the electrochemical gradient. Approximately 50% of the brain's total energy consumption is used to restore ion gradients and resting membrane potentials through the action of Na^+/K^+-ATPase (Ames, 2000). It is estimated that action potentials and the postsynaptic effects of glutamate account for the majority of the brain's energy consumption (47% and 34%, respectively), with the resting potential representing a smaller

amount (13%), and glutamate recycling only 3% (Attwell *et al.*, 2001) (see Fig. 1).

With less ATP and less EAATs, the astrocyte cannot respond as quickly to stimulation (concentration, speed), particularly to the capture of glutamate and the results of a kinetic imbalance. The consequence is a temporal imbalance between the frequency of action potentials and kinetics of inputs and outputs of glutamate, Ca^{2+}, Na^{+} and K^{+} for glutamatergic synapses. On the one hand, the balanced reaction velocities between the Na^{+}/K^{+}-ATPase and loss of potassium by ion channels (voltage dependent) are fundamental. This drives the membrane polarization-depolarization. Reducing the driving force for Na^{+}-dependent glutamate clearance increases the residence time of glutamate in the synaptic cleft, thereby increasing glutamate concentrations. On the other hand, this increased synaptic glutamate causes excessive stimulation of the glutamate receptors (NMDA receptor, AMPA receptor). The result gives rise to increased intracellular Ca^{2+} concentrations. The initial glutamate receptor opening of the Na^{+}/Ca^{2+} channels not only allows the influx of Ca^{2+}, but it also causes membrane depolarization. This depolarization in turn activates the voltage-dependent Ca^{2+} channels, which further increases intracellular Ca^{2+} levels. ATP depletion and the reduced sodium gradient across the cell membrane – caused by the glutamate receptor-coupled channels – impair the cell's ability to remove intracellular calcium (Ca^{2+}-ATPase, Na^{+}/Ca^{2+} antiporter). Thus, a slowdown in ATP production kinetics for ATPases (pumps) has consequences on the rate of membrane polarization and action potential, on one hand, and the maintenance of extracellular Ca^{2+} levels, on the other hand, leading to desynchronization (see Fig. 1).

The activation of BDNF (Brain-derived neurotrophic factor) helps to stimulate the PI3K/Akt signaling pathway and upregulates NMDA receptor activity. In short, high-frequency neuronal activity induces the secretion of BDNF, whose presence boosts this important pathway mediated by IGF-1 and estradiol (Majou and Dermenghem, 2024b). Dendritic release of BDNF is activity-dependent, based on calcium influx, so the action of BDNF appears to inhibit epileptinogenesis. However, PPAR-RXR binds to the PPRE and activates the *BDNF* gene *via* the *CREB* gene (cyclical AMP response element binding protein) and the CREB protein (Majou and Dermenghem, 2024b). DHA is a preferential ligand for PPARs and RXRs (de Urquiza *et al.*, 2000; Diep *et al.*, 2002; Deckelbaum *et al.*, 2006; Song *et al.*, 2017; Dziedzic *et al.*, 2018). As a result, BDNF levels are low when DHA is depleted. A clinical study in patients with temporal lobe epilepsy showed that serum BDNF levels in patients with temporal lobe epilepsy were significantly lower than those in healthy controls, with a negative correlation between BDNF serum levels and the duration of epilepsy (Wang *et al.*, 2021). If regional neuronal stimulation is low, BDNF cannot effectively activate the MAPK and PI3K/Akt pathways. Moreover, DHA depletion lowers *BDNF* gene transcription *via* CREB.

4 The effects of a seizure

Epileptic seizures increase cerebral blood flow — as well as oxygen and glucose uptake (Bahar *et al.*, 2006; Bode, 1992; Brodersen *et al.*, 1973; De Simone *et al.*, 1998; Duncan, 1992; Meldrum and Nilsson, 1976) — and are accompanied by local vasodilatation. This phenomenon is associated not only with the pathological synchronization of neurons but also with the slow depolarization of the astrocyte membrane. Electroconvulsive seizures cause a rapid elevation in astrocyte endfoot Ca^{2+}. Vascular smooth muscle cells exhibit a significant increase in Ca^{2+} both during and following seizures (Volnova *et al.*, 2020). Nitric oxide (NO) relaxes vascular smooth muscles. It is produced by a group of enzymes called nitric oxide synthases (NOS). Three NOS isoforms have been identified: neuronal NOS (nNOS), endothelial NOS (eNOS), and inducible NOS (iNOS) present in cerebral vascular endothelial cells, motor neurons, dendritic spines (Caviedes *et al.*, 2017) and astrocytes (Wiencken *et al.*, 1999). During physiological processes, NO produced by both eNOS and nNOS controls blood flow activation through vasodilatory responses (Reis *et al.*, 2017). eNOS becomes more prominent at lower levels of neuronal activity, whereas nNOS dominates at higher neuronal activation levels (de Labra *et al.*, 2009). We have described the mechanisms of local vasodilatation (Majou and Dermenghem, 2023). The phosphorylation of eNOS resembles that of AS160 *via* the activation/phosphorylation of AMP-activated protein kinase (AMPK) or *via* the PI3K (phosphoinositide-3-kinase)/Akt signaling pathway. The first pathway, *via* AMPK, is most commonly induced upon activation of the NMDA receptor, which results in a calcium influx (Zonta *et al.*, 2003; Stobart *et al.*, 2013). The pathway leads to a dilation of local parenchymal arterioles that meets the increased metabolic demand. NO is known as the endothelium-relaxing derived factor (ERDF). NO is synthesized at astrocytes and postsynaptic neurons (Galea *et al.*, 1992; Ko *et al.*, 1999).

We can assume that vasodilatation and increased cerebral blood flow prioritizes the delivery of nutrients to the seizure zone (Roy and Sherrington, 1890). These nutrients include DHA and glucose (see Fig. 1). This increased supply of DHA may support (i) an increase in BDNF mRNA levels (Isackson *et al.*, 1991; Nibuya *et al.*, 1995), which helps to stimulate the IRS-1/PI3K/Akt signaling pathway and upregulates NMDA receptor activity (Majou and Dermenghem, 2024b), (ii) a reduction in soluble Aβs according to the process described above, maybe even removing all residual Aβs, contributing to the resolution of epilepsy. The extent of the clearance depends on the initial concentration. This clearance allows Aβ levels to fall below the threshold. The initial Aβ concentration and the rate at which it re-accumulates determines the interval between seizures. The seizure allows the total or partial elimination of toxic Aβ residues. We can also assume that the TREK-1 potassium channel is involved. The supply of DHA *via* vasodilatation appears to activate TREK-1 (Bechard *et al.*, 2024) and induce the hyperpolarization of neurons, leading to a decreased activation of the synaptic cleft. At the postsynaptic level, hyperpolarization reduces the activation of the glutamate receptor NMDA (magnesium ion blocking). The result of this is reduced glutamatergic transmission and excitotoxicity (Heurteaux and Blondeau, 2005) (Fig. 1).

5 Children at risk and detection

Children at risk are those exposed to an initial triggering factor, perinatal pain, which gives rise to cryptic lesions,

followed by a second triggering factor, soluble amyloid β, generated as a consequence of these cryptic lesions. These two triggering factors are compounded by two aggravating factors: DHA dyslipidemia in the mother, which is transmitted to the fetus and the child. In humans, the accumulation of DHA in the central nervous system occurs primarily during the last trimester, through placental transfer, as well as in the first 18 postnatal months (Martinez, 1991) (Innis, 2005). Preformed DHA is passed from the mother to the fetus prenatally *in utero* (Dutta-Roy, 2000). After birth, DHA is transferred from the mother to the infant through breast milk (Putnam *et al.*, 1982). While the overall diet can alter the fatty acid composition of maternal breast milk, on average, the fatty acid composition of breast milk consists of DHA (0.3-0.6%), ARA (0.4-0.7%), linoleic acid (8-17%), and α-linolenic acid (0.5-1%) (Barcelo-Coblijn and Murphy, 2009). However, it is hypothesized that the optimal DHA level for breast milk is 0.8% of total fatty acids (a level at which plasma and red blood cell DHA levels in infants reach their peak) (Gibson *et al.*, 1997). These concentrations depend on dietary omega-3 and omega-6 intake. High linoleic acid intake during pregnancy is especially hazardous as it lowers EPA/DHA in the umbilical plasma and vein vessel walls and reduces the availability of DHA to the growing fetus (Al *et al.*, 1996).

During the perinatal stage, this DHA deficiency comes from the mother's diet, either due to an insufficient intake of alpha-linolenic acid (ALA), a precursor of EPA and DHA, or a competition between the elevated quantities of omega-6, omega-9, and omega-3 precursors that use the Δ6-desaturase for their conversion, respectively competition between linoleic acid, palmitic acid, and α-linolenic acid – this competition exacerbates DHA deficiency (Park *et al.*, 2016) – or genetically due to polymorphisms on the *FADS2* Δ6-desaturase gene. In a recent article, we described the mechanisms of supply of DHA in astrocytes and neurons (Majou and Dermenghem, 2023). The brain is capable of autonomous DHA synthesis in the astrocytes from dietary ALA *via* the blood-brain barrier. However, it prefers an exogenous source of DHA, directly from the diet, *via* the blood brain barrier (Ouellet *et al.*, 2009), or by synthesis in the liver from dietary ALA, but only 5% ALA is converted into DHA. A more efficient route for the incorporation of DHA into brain lipids is *via* DHA itself, derived from food, or phospholipids, or by metabolism in the liver, rather than by metabolism from ALA in astrocytes (Sinclair *et al.*, 1972). DHA is synthesized from dietary ALA through a series of enzyme transformations, including two desaturases (Δ6-desaturase and Δ5-desaturase) and elongases in the endoplasmic reticulum, followed by peroxisomal β-oxidation (Voss *et al.*, 1991). Δ6-desaturase catalyzes two essential stages of DHA biosynthesis (Cho *et al.*, 1999; Stoffel *et al.*, 2008). As the second stage of desaturation by this enzyme is limiting, this makes Δ6-desaturase a key enzyme in DHA synthesis (Lattka *et al.*, 2010; Tosi *et al.*, 2014; O'Neill *et al.*, 2017; Delplanque, 2017). In humans, the *FADS2* gene (*Δ6-desaturase* gene) is expressed ubiquitously, especially in the liver and brain (astrocytes) (Innis *et al.*, 2002; Nakamura *et al.*, 2004).

Although food-based DHA plays a direct role on its plasma and erythrocytic levels, genetic factors have an important role in influencing DHA concentrations in human tissue through an ALA-rich diet. The *FADS1* and *FADS2* genes code for Δ5-desaturase and Δ6-desaturase, respectively. In the NCBI SNP database, more than 3,200 simple nucleotidic polymorphisms (SNPs) are referenced on *FADS2* for *Homo sapiens*. Some studies have shown a close correlation between several SNPs in the *FADS1* and *FADS2* genes and concentrations of omega-3 and −6 fatty acids (Schaeffer *et al.*, 2006; Xie and Innis, 2008; Rzehak *et al.*, 2009; Glaser *et al.*, 2011). Homozygous carriers of different minor alleles have higher desaturase substrates (α-linolenic acid, linoleic acid) and lower levels of desaturation products (DHA, EPA, ARA) (Glaser *et al.*, 2011; Lankinen *et al.*, 2018). This suggests reduced desaturase expression in individuals with these polymorphisms (Moltó-Puigmartí *et al.*, 2010). In our opinion review (Majou, 2021), we speculated that SNPs, especially those on PPRE, modulate the binding affinity of the DHA-PPARα-RXRα-DHA heterodimer on PPRE. Maternal and child genotypes were equally associated with DHA in neonatal cord blood, which reflects both placental transfer and fetal metabolism of DHA (Koletzko *et al.*, 2011; Tanjung *et al.*, 2018). Maternal DHA and EPA status during gestation influences maternal-to-infant transfer, and breast milk provides fatty acids for infants after birth. Genetic variants of *FADS1* and *FADS2* influence blood lipid and breast milk essential fatty acids during pregnancy and lactation (Xie and Innis, 2008). The lactating mammary gland has the capacity to synthesize PUFAs (Rodriguez-Cruz *et al.*, 2006).

It should be noted that in our previous articles, and in this one, we often mention the important role of PPAR-RXR heterodimers in seizure control through their interaction with their ligands, DHA. These assertions seem to be confirmed by several animal studies showing that selective agonists of PPARα and PPARɣ — such as fenofibrate, a potent inducer of PPARα (Porta *et al.*, 2009), or FMOC-L-Leucine with PPARɣ (Maurois *et al.*, 2008) — raise seizure thresholds.

Children born prematurely miss peak accumulation of DHA from the mother and certain infant formulas only provide linoleic acid and ALA, whereas breast milk also provides DHA. Therefore, premature babies who are formula-fed may be at particular risk of DHA deficiency (DiNicolantonio and Keefe, 2020; Hoffman et Uauy, 1992). To meet these infants' specific DHA requirements, it is recommended to increase the DHA content of breast milk by providing their mothers with a DHA supplement (Lapillonne and Jensen, 2009).

In order to anticipate epilepsy in children, it would be useful to draw up a questionnaire on the child's medical history. Perinatal suffering is not always recorded in the history of epilepsy, when it is minimal or very minimal or discreet, with no alarming signs (hypothermia, for example, responsible for vasoconstriction) resulting from prolonged labor. It is important to also detect the cases that do not result from acute suffering. Risk factors can be identified from the patient's medical history based on the conditions of childbirth and the dangers of neonatal hypoxia without apparent lesions (difficult delivery, fetal suffering, nuchal cord, premature birth, twins, etc.), with clinical, anatomical and functional data. The questionnaire could be completed with questions on clinical signs that may also point to a DHA deficiency:

- xeroderma in the mother, child or siblings (atopic dermatitis caused by a lack of sapienic acid synthetized by Δ6-desaturase (Majou, 2018);
- asthma, atopic rhinitis;

– overactivity, anxiety;
– breastfeeding;
– DHA/EPA supplementation (breastfeeding and infant milk).

The questionnaire should be complemented by the determination of fatty acids in erythrocytes (with levels of DHA, EPA, ALA, LA, and ARA) including the ratio of omega-3 fatty acids to omega-6 fatty acids. If a lipid abnormality exists, family screening, particularly of the mother, would be useful to assess the hereditary dimension of this dyslipidemia, whether or not it is associated with symptoms of xeroderma.

6 DHA treatment and prevention

As previously discussed, DHA deficiency is an aggravating factor in the reduction of Aβ levels and glucose and ascorbic acid supply in response to stimuli. DHA has been found to have anticonvulsant properties and to reduce seizures in several animal models (Ferrari *et al.*, 2008; Gavzan *et al.*, 2018; Moezifar *et al.*, 2019; Scorza *et al.*, 2009; Taha *et al.*, 2010; Trepanier *et al.*, 2012; Wang *et al.*, 2022; Yang *et al.*, 2023; Yonezawa *et al.*, 2023). Some studies demonstrate that EPA and DHA are effective in reducing the frequency of seizures in patients with drug-resistant epilepsy (DeGiorgio *et al.*, 2015; Ibrahim *et al.*, 2018). Seizure frequency and duration were reduced after the completion of the treatment in the supplement groups (Yuen *et al.*, 2005; Bromfield *et al.*, 2008; Al Khayat *et al.*, 2010; Ishihara *et al.*, 2017; Omrani *et al.*, 2019). The same applies to fish oils. Omega 3 polyunsaturated fatty acids elevate the seizure threshold in epileptic patients and may help in achieving seizure control (Schlanger *et al.*, 2002; Reda *et al.*, 2015). Children who received omega-3 supplements showed a significant decrease in the frequency of seizure attacks after six months of supplementation compared to the baseline before supplementation ($P < 0.05$) (Elsadek *et al.*, 2021). Prior to oral PUFA supplementation, patients with intractable epilepsy had lower levels of DHA and higher levels of ALA compared to controls (Al Khayat *et al.*, 2010); this clearly shows a lack of Δ6-desaturase productivity. The authors have personal experience of two epileptic children and one adolescent — one child (5 years old) with no drug treatment, one child (12 years old) on micropakine (1.5 mg/day), and one adolescent (15 years old) — whose seizures stopped after treatment with DHA/EPA (250-500 mg/day) (unpublished results).

DHA dyslipidemia in mother and child, caused by *FADS2* variants and low dietary DHA intake or ALA intake (Couedelo *et al.*, 2022), can be entirely or partially offset, depending on the dose provided by dietary DHA intake and nutritional supplements (*e.g.* capsules) (Helland *et al.*, 2006; Innis and Friesen, 2008; Krauss-Etschmann *et al.*, 2007). Depending on the level of dyslipidemia, a DHA intake of 120-160 mg/day is quite beneficial (Morris *et al.*, 2003). Moreover, the combination of DHA + EPA (fish oils) is also pertinent (Van Gelder *et al.*, 2007; Swanson *et al.*, 2012) in ratios of about 1:3, or 120-160 mg DHA/day and 360-480 mg EPA/day. Indeed, EPA can compete with DHA as a PPARα ligand for the transcription of *FADS2* (Deckelbaum *et al.*, 2006). EPA reduces inhibition by DHA (Majou, 2021). This is particularly important in the case of *FADS2* alleles that are inhibited with lower DHA concentrations.

Children at risk of epilepsy could be given DHA supplements from birth. If the child is breastfed, mothers whose milk is deficient in DHA should be supplemented with DHA to enrich their milk (Juber *et al.*, 2017). If the infant is fed with formula, it should be enriched with DHA. Then, when the child is weaned, it should receive DHA supplements (capsules). As described above, DHA enrichment prevents the synthesis of Aβs (non-amyloidogenic pathway), suppresses soluble Aβs already formed, and greatly improves the flow rate of GLUT-1 transporters (glucose, ascorbic acid precursor). As a result, it cancels out the second trigger of epilepsy. This approach makes it possible to prevent the onset of idiopathic focal epilepsy.

7 Conclusion

This opinion review describes the pathogenetic mechanisms behind epilepsy, as well as its triggering and aggravating factors. A triggering factor is a perinatal pain (hypoxia) that generates amyloid-β peptide oligomers that are not eliminated. An aggravating factor is a deficiency of DHA — due to diet or specific FADS2 alleles (Δ6-desaturase gene) — which is a preferential ligand of the PPARα-RXRα and PPARɣ-RXRα heterodimers. These two factors have impacts on the glutamatergic pathways: (i) metabolic homeostasis as a function of stimulation (regional blood flow); (ii) flow rate of GLUT-1 transporters (glucose, ascorbic acid precursor); (iii) regulation of oxidative stress; (iv) repair of oxidative injuries; (v) priority given to the non-amyloidogenic pathway; (vi) proteolysis of Aβ residues and their removal. The originality of this approach resides in particular in highlighting the fundamental role played by DHA. Individual paediatric interventions have demonstrated the positive effects of DHA and EPA supplementation. It is now essential to confirm these results through a randomised, double-blind, placebo-controlled intervention study involving 300 children over a period of approximately 12 weeks.

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