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# F<sub>4</sub>-neuroprostanes and F<sub>2</sub>-dihomo-isoprostanes: biomarkers and bioactive oxylipins

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**Abstract** – Under condition of oxidative stress, free radical-catalyzed peroxidation of docosahexaenoic acid (DHA) and adrenic acid (AdA) generates *in vivo* neuroprostanes (NeuroPs) and dihom-isoprostanes (dihomo-IsoPs), among a large number of key products participating in many pathophysiological processes. These non-enzymatic oxygenated metabolites display a wide range of biological actions (especially DHA-metabolites), and some of them are now considered as the most reliable indicators of oxidative stress in neurodegenerative, neurodevelopmental or cardiovascular diseases. In this review, we will present an overview regarding neuroprostanes and dihom-isoprostanes and discuss about their biological interests.

**Keywords:** biomarkers / docosahexaenoic acid / radical peroxidation / neuroprostanes / dihom-isoprostanes / bioactive oxylipins / total synthesis

**Résumé** – F<sub>4</sub>-neuroprostanes et F<sub>2</sub>-dihomo-isoprostanes : biomarqueurs et oxylipines bioactives. Dans des conditions de stress oxydatif, la peroxydation, catalysée par les radicaux libres de l'acide docosahexaénoïque (DHA) et de l'acide adrénique (AdA) génère, parmi un grand nombre de produits clés participant à de nombreux processus physiopathologiques, des neuroprostanes (NeuroPs) et dihom-isoprostanes (dihomo-IsoPs). Ces métabolites oxygénés non-enzymatiques présentent de nombreuses activités biologiques, et certains d'entre eux sont désormais considérés comme les biomarqueurs les plus fiables du stress oxydatif dans les maladies neurogénéralives, neurodéveloppementales ou encore cardiovasculaires. Dans cette revue, seront présentés les différents travaux autour des neuroprostanes et dihom-isoprostanes, et notamment leur intérêt biologique.

**Mots clés** : biomarqueurs / activités biologiques / peroxydation lipidique / acides gras polyinsaturés / neuroprostanes / dihom-isoprostanes

## 1 Introduction

In 1990, [Morrow \*et al.\* \(1990\)](#) highlighted the formation in man of the isoprostanes (IsoPs), isomeric to prostaglandins (PGs), by a non-enzymatic mechanism involving the radical peroxidation. These compounds are biosynthesized while arachidonic acid (C20:4 n-6, AA) is linked to the phospholipids. A large number of diastereoisomers, however with major *cis*-configurations between the lateral chains on the cyclopentane ring, can be generated, as well as several functions on the 5-member ring (diol, enone, hydroxyketone). The metabolites are further released from the membrane by a specific phospholipase A<sub>2</sub> (PLA<sub>2</sub>) ([Stafforini \*et al.\*, 2006](#)).

Later, the same group from the Vanderbilt University described a similar mechanism for the peroxidation of docosahexaenoic acid (C22:6 n-3, DHA), one of the main polyunsaturated fatty acids (PUFAs) in the brain, leading to neuroprostanes (NeuroPs) ([Roberts \*et al.\*, 1998](#); [Nourooz-Zadeh \*et al.\*, 1998](#)).

It should be known that the lipid peroxidation of PUFAs (here DHA, [Fig. 1](#)) begins with the abstraction of an atom of hydrogen by HO<sup>•</sup>, in one of the 5 bis-allylic positions, either on C-5, or C-8, or C-12 or C-15 or C-18. The pentadienyl radical formed reacts with a molecule of dioxygen to form a peroxy radical which undergoes a cyclization and the subsequent radical formed reacts with a second molecular oxygen molecule to generate a hydroperoxide. Finally, a complete reduction yields the whole family of F<sub>4</sub>-NeuroPs with several series (4, 7, 10, 11, 13, 14, 17, and 20) ([Fig. 1](#)), when the partial

<sup>a</sup> Chevreul Medal 2018.

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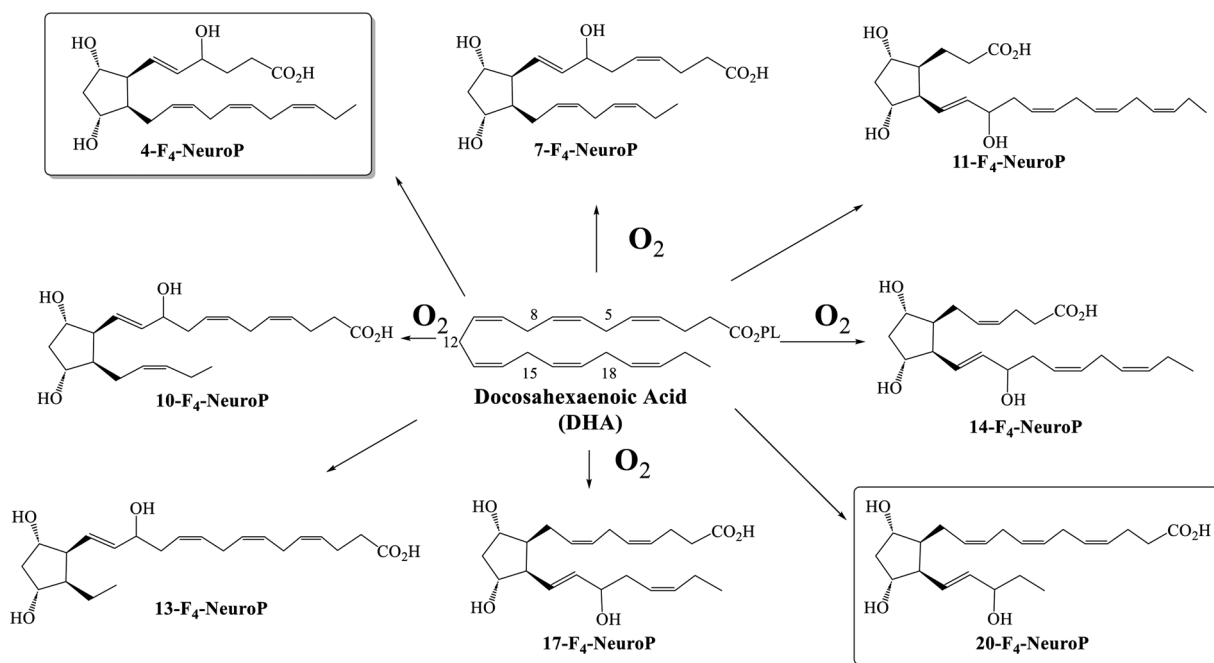


Fig. 1. F<sub>4</sub>-NeuroP products of DHA peroxidation.

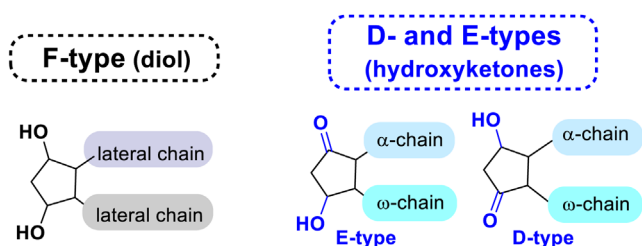


Fig. 2. E- and D- type products of PUFA peroxidation.

reduction yields the D<sub>4</sub>- and E<sub>4</sub>-NeuroPs (hydroxyketone function of the cyclic ring) (Fig. 2). Note that these metabolites are produced as racemic *in vivo*.

The increase of the F<sub>4</sub>-NeuroP concentration is demonstrated in several pathologies as for example the neurodegenerative and cardiovascular diseases, and they are now considered as the best markers of the lipid peroxidation. Their quantification in urine and plasma allows a precise, non-invasive and representative measure of oxidative stress (Milne *et al.*, 2007; Mas *et al.*, 2008; Michel *et al.*, 2008; Vigor *et al.*, 2014).

The quantification processes were developed thanks to the availability of synthetic compounds provided by organic chemists able to produce large amount of pure compounds (Jahn *et al.*, 2008). Furthermore, some metabolites that became commercially available were studied and a lot of biological activities were reported over the years (Galano *et al.*, 2017; Ahmed *et al.*, 2020). For example, to determine whether IsoP structures possessed intrinsic biological activities, Morrow *et al.* (1990) have tested the 15-F<sub>2</sub>-IsoP to study blood pressure. The metabolite was injected in a rat kidney, in the peripheral vein or directly in the kidney, and a reduction of the blood pressure as well as the rate of filtration was observed. IsoPs and other PUFA metabolites thus have biological

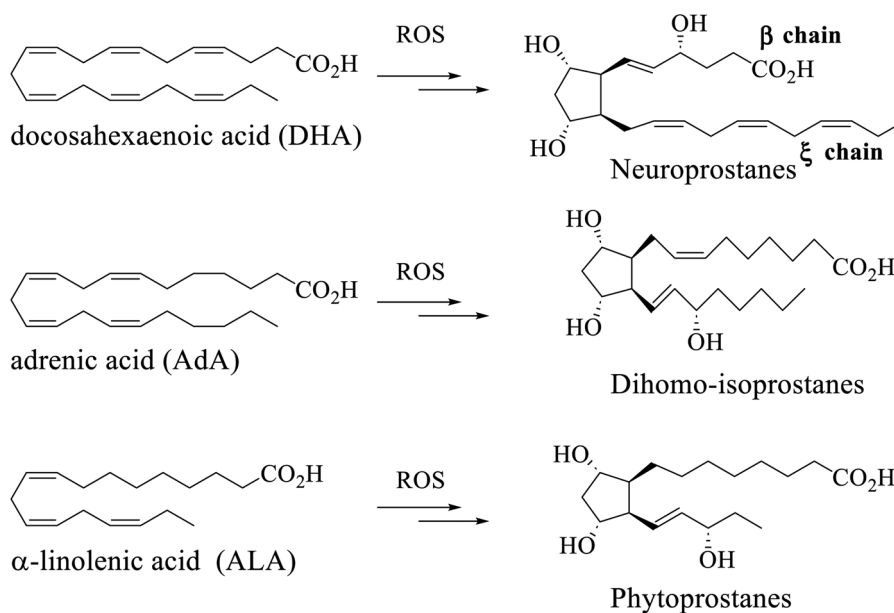
activities which confer them a role of mediator in a context of OS (Galano *et al.*, 2017; Ahmed *et al.*, 2020).

In mammals, this prolific pathway can occur with different PUFAs (Fig. 3). If DHA is enriched in the grey matter and retina, and yields to neuroprostanes (NeuroPs) after peroxidation (Roberts *et al.*, 1998; Nourooz-Zadeh *et al.*, 1998), another PUFA, adrenic acid (AdA, C22:4 n-6) is mainly present in the myelin (white matter) and retina and produces another class of metabolite, the dihom-Isoprostanes (dihomo-IsoPs) (Song *et al.*, 2008; VanRollins *et al.*, 2008; De La Torre *et al.*, 2014, 2015; De Felice *et al.*, 2011). In plants, the phytoprostanes (PhytoPs) were described, resulting from the radical peroxidation of  $\alpha$ -linolenic acid (ALA, C18:3 n-3) (Imbusch and Mueller, 2000). It should be mentioned that twelve years after the discovery of the IsoPs, Fessel *et al.* (2002) have highlighted a new class of metabolites containing a tetrahydrofuran core and named them isofurans (IsoFs). Later, neurofurans (NeuroFs) (De La Torre *et al.*, 2015) and dihomo-isofurans (dihomo-IsoFs) were detected (De La Torre *et al.*, 2014).

The lovely story of some of these molecules, especially NeuroPs and dihomo-IsoPs will be presented in this review. Several outcomes in terms of syntheses, diagnosis and biological activities, gathering almost thirty years of research, from organic chemistry knowledge through a smart multi-step synthesis strategy providing many pure compounds, to our fruitful collaborations with a large number of scientists, biologists, clinicians all around the world (Galano *et al.*, 2013, 2015).

## 2 Chemical synthesis

Since the discovery of IsoPs, our group among other developed several strategies to access PUFA metabolites with high purity and enantioselectivity (Vigor *et al.*, 2022).



**Fig. 3.** Metabolites resulting of the radical peroxidation of PUFAs.

Nowadays, in our group we are using the last, simple and highly stereocontrolled strategy developed in 2008 (Oger *et al.*, 2008). This strategy is based on a bicyclic  $\alpha,\beta$ -epoxy ketone intermediate (Fig. 4). To this core, and as the key steps, Horner–Wadworth–Emmons and Wittig reactions permit to plug the large diversity of lateral chains, thanks to the synthesis of the appropriate phosphonium salts or phosphonates. The allylic alcohol on the lateral chain is obtained either as (*R*) or (*S*)-epimer thanks to an enantioselective chemical reduction. These strategies have allowed us to access IsoPs, dihom-IsoPs, NeuroPs and other PhytoPs metabolites (Fig. 4) (Brinkmann *et al.*, 2010; Oger *et al.*, 2010a, b, 2012; Guy *et al.*, 2014).

### 3 New biomarkers

The best technic for the analysis of such metabolites is the tandem chromatography-mass spectrometry, whether using gas or liquid chromatograph (GC-MS, LC-MS). Thanks to the development of MS<sup>2</sup>, GC-MS/MS and LC-MS/MS technics are therefore more specific and sensitive, and allow quantification of particular metabolites found in low abundance in different sample matrices. Both GC-MS/MS and LC-MS/MS have been used for quantification of a wide range of isoprostanoids. However, the derivatization process required for GC-MS analysis to improve the volatility and thermal stability of the compounds is often time-consuming and lead to low recovery yields. Indeed, this derivatization process needs to convert the carboxylic acid into pentafluorobenzyl esters (PFB) by pentafluorobenzyl bromide (PFBB) in the presence of a catalyst such as *N,N'*-diisopropylethylamine, and the hydroxyl functions with either *O-bis* (trimethylsilyl) trifluoroacetamide + 1% trimethylchlorosilane (BSTFA+TMCS) or *N-Methyl-N*-trimethylsilyltrifluoroacetamide (Vigor *et al.*, 2014) to form trimethylsilyl ether derivatives.

However, derivatization is not a mandatory for LC-MS technic. Therefore, several methods were developed for LC-MS/MS studies of PUFA metabolites (Collado-Gonzales *et al.*, 2015; Lee *et al.*, 2016; Sánchez-Illana *et al.*, 2017; Rund *et al.*, 2018). As for example, our group in collaboration with the group of Justine Bertrand-Michel was able to detect and quantify more than 50 isoprostanoids synthesized in our group, in a run a 20 min (Fig. 5) (Dupuy *et al.*, 2016). It should be mentioned that depending of the series of isoprostanoids, this method permits to separate the two epimers of the allylic alcohol (Fig. 6). In this sense, the development of new technic and/or methods to separate diastereoisomers of PUFA metabolites is still of great interest.

#### 3.1 Neuroprostanes

Our two first examples reporting the interest of F<sub>4</sub>-NeuroPs as biomarkers of pathological states were performed by Barden *et al.* (1996, 2004, 2012). In a recent study F<sub>4</sub>-NeuroPs, F<sub>2</sub>-IsoPs as well as IsoFs were quantified in maternal plasma and cord blood of women with pre-eclampsia and normal pregnancy. Women with pre-eclampsia had significantly elevated maternal IsoFs and F<sub>4</sub>-NeuroPs, but no F<sub>2</sub>-IsoPs. Cord blood F<sub>4</sub>-NeuroPs were elevated among neonates of mother with pre-eclampsia. Interestingly, cord blood IsoFs were approximately 5-fold higher than those found in maternal plasma. This could reflect the oxidative challenge presented at birth when there is transition from a relatively low intra-uterine oxygen environment to a significantly higher extra uterine oxygen environment. Maternal F<sub>4</sub>-NeuroPs were not significantly correlated with cord blood F<sub>4</sub>-NeuroPs in pre-eclamptic and in normal pregnancies, suggesting the origin of cord F<sub>4</sub>-NeuroPs may be independent of maternal plasma. In normal pregnancy, birth weight was negatively related to maternal F<sub>2</sub>-IsoPs, IsoFs and F<sub>4</sub>-NeuroPs.

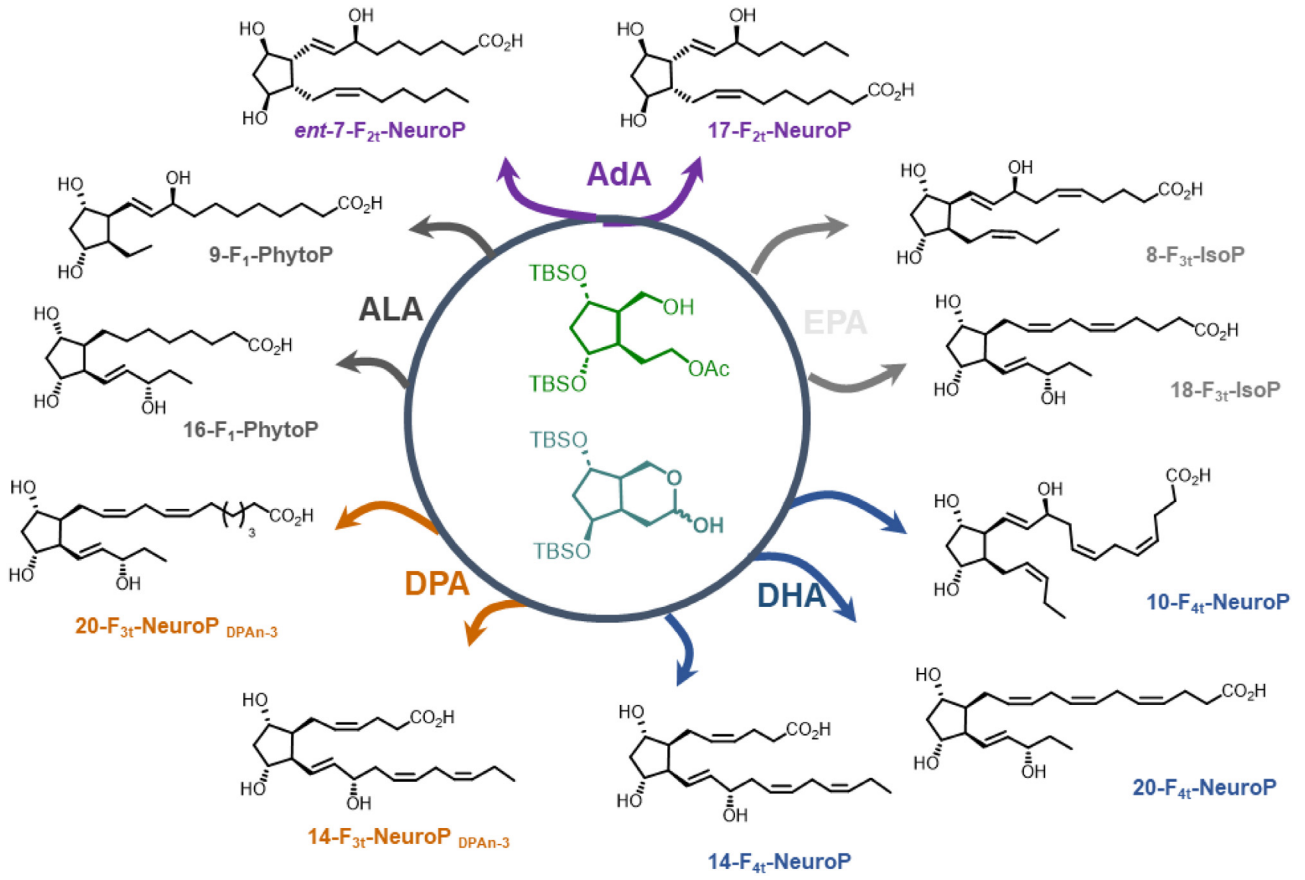


Fig. 4. A fully flexible approach.

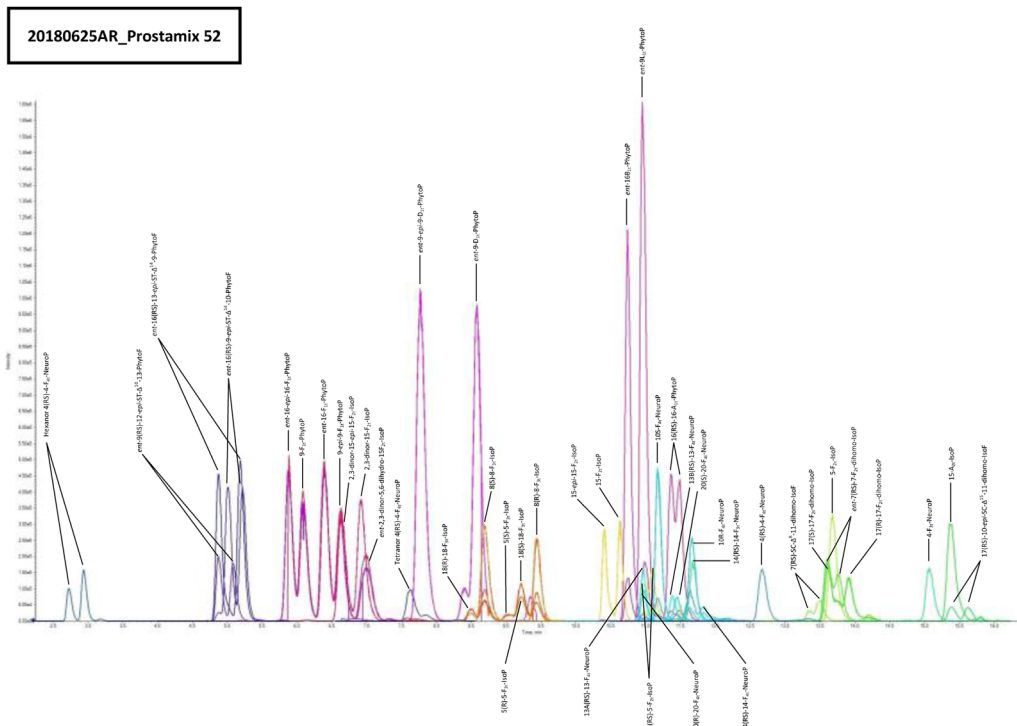
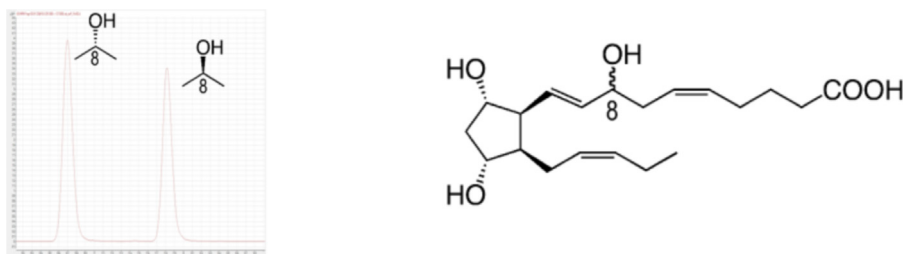


Fig. 5. LC-MS/MS > 50 isoprostanooids.



**Fig. 6.** Epimer separation for the 8(*RS*)-8-F<sub>3</sub>I-IsoP.

The brain is vulnerable to oxidative insult because of high oxygen requirements for its metabolism and high PUFA composition, in particular DHA. Thus, F<sub>4</sub>-NeuroPs are considered as specific markers of brain OS. Aneurysmal subarachnoid hemorrhage (aSAH) and traumatic brain injury (TBI) are associated with devastating central nervous system (CNS) injury. Two case-controlled studies have shown a significant increase in cerebrospinal fluid (CSF) of IsoFs in aSAH and TBI patients compared with their respective age- and gender-matched controls. aSAH patients also had significantly increased levels of CSF F<sub>4</sub>-NeuroPs and F<sub>2</sub>-IsoPs. Patients with TBI had significantly increased CSF F<sub>4</sub>-NeuroPs but F<sub>2</sub>-IsoPs were similar to control (Corcoran *et al.*, 2011). These data confirm that CNS injury, in case of aSAH or TBI, results in increased OS and as DHA is the brain major PUFA, F<sub>4</sub>-NeuroP levels in CSF could be a much more specific indicator of neurological dysfunction than F<sub>2</sub>-IsoPs. Hsieh *et al.* (2009) have showed that increased F<sub>4</sub>-NeuroPs in CSF of patients with aSAH correlated with poor neurological outcome. They suggested that F<sub>4</sub>-NeuroPs might be more useful than F<sub>2</sub>-IsoPs in CSF to predict outcome and interpret the role of hemorrhage in aSAH. Although Farias *et al.* (2008) showed increased F<sub>2</sub>-IsoPs during rat brain ischemia, the E<sub>2</sub>/D<sub>2</sub>-IsoPs were increased to a greater extent, suggesting the latter may better markers of OS in brain ischemia.

The anti-atherogenic effects of omega-3 fatty acids, eicosapentaenoic acid (EPA, C<sub>20</sub>:5 n-3) and DHA are well recognized but the impact of dietary intake on bioactive lipid mediator profiles remains unclear. Such a profiling effort may offer novel targets for future studies into the mechanism of action of omega-3 fatty acids. Gladine *et al.* (2014) studied the impact of DHA supplementation on the profiles of PUFA oxygenated metabolites and their contribution to atherosclerosis prevention. A special emphasis was given to the non-enzymatic metabolites knowing the high susceptibility of DHA to free radical-mediated peroxidation, and the increased OS associated with plaque formation. Atherosclerosis prone mice (LDLR<sup>2/2</sup>) received increasing doses of DHA (0, 0.1, 1 or 2% of energy) during 20 weeks leading to a dose-dependent reduction of atherosclerosis ( $R^2=0.97$ ,  $p=0.02$ ), triglyceridemia ( $R^2=0.97$ ,  $p=0.01$ ) and cholesterolemia ( $R^2=0.96$ ,  $p<0.01$ ). Targeted lipidomic analyses revealed that both the profiles of EPA and DHA and their corresponding oxygenated metabolites were substantially modulated in plasma and liver. Notably, the hepatic level of F<sub>4</sub>-NeuroPs was strongly correlated with the hepatic DHA level. Moreover, unbiased statistical analysis including correlation analyses, hierarchical cluster and projection to latent structure discriminate analysis revealed that the hepatic level of F<sub>4</sub>-NeuroPs was the variable

most negatively correlated with the plaque extent ( $p<0.001$ ) and along with plasma EPA dihydroxylated metabolites was an important mathematical positive predictor of atherosclerosis prevention. Thus, oxygenated n-3 PUFA, and F<sub>4</sub>-NeuroPs, are potential biomarkers of DHA-associated atherosclerosis prevention. While these may contribute to the anti-atherogenic effects of DHA, further *in vitro* investigations are needed to confirm such a contention and to decipher the molecular mechanisms of action.

### 3.2 Dihomo-isoprostanes

Rett syndrome (RTT) is a pervasive abnormality of development affecting almost exclusively females, which is included among the autism spectrum disorders. RTT is caused in up to 95% of cases by mutations in the X-linked methyl-CpG binding protein 2 (MeCP2) genes (De Felice *et al.*, 2012). Although over 200 different MeCP2 mutations have been reported to cause RTT, nine most frequent ones (hotspot mutations) are known to comprise more than three quarters of all the reported pathogenic mutations. The disease shows a wide phenotypical heterogeneity, with at least 4 distinct major clinical presentations, *i.e.*, typical, preserved speech, early seizure variant, and congenital variant. First, clinical evidence indicates that F<sub>2</sub>-IsoPs and F<sub>4</sub>-NeuroPs are involved in the intimate pathogenetic mechanisms of RTT (De Felice *et al.*, 2011). Plasma levels of free F<sub>2</sub>-IsoPs are significantly higher in the early stages of RTT, as compared with the late natural progression of typical RTT. Until 2011, it was thought that the predominant central nervous system damage in RTT occurred in gray matter. However, the relative abundance in myelin of the precursor AdA and the increased level of F<sub>2</sub>-dihomo-IsoPs, strongly confirm an early and severe damage to the brain white matter as suggested by previous brain MRI evidence (De Felice *et al.*, 2011). Thus F<sub>2</sub>-dihomo-IsoPs can be considered early markers of lipid peroxidation in RTT. F<sub>4</sub>-NeuroPs also appear to be important biomarkers in RTT. Plasma F<sub>4</sub>-NeuroPs levels correlate with disease severity in RTT and are significantly related to neurological symptoms severity, mutation type and clinical presentation. Therefore, F<sub>4</sub>-NeuroPs may also play a major role along the biochemical pathway from MeCP2 gene mutation to clinical evidence, proving that a DHA oxidation process occurs (Cortelazzo *et al.*, 2016).

The same group, De Felice and Signorini reported the importance of neuroprostanes and dihydro-isoprostanes in different neurological diseases (Signorini *et al.*, 2018), KRABBE disease (Signorini *et al.*, 2019), cerebral adrenoleukodystrophy disease (Signorini *et al.*, 2022) and finally in sperm capacitation (Signorini *et al.*, 2021).

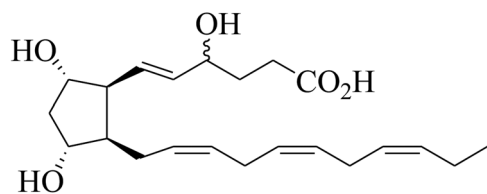


Fig. 7. 4(RS)-4-F<sub>4t</sub>-NeuroP.

Finally, Vento and collaborators reported also the importance of neuroprostanes and dihomio-isoprostanes in Alzheimer disease and newborns (Garcia-Blanco *et al.*, 2018; Peña-Bautista *et al.*, 2019; Cascant-Vilaplana *et al.*, 2021).

## 4 New bioactive lipids

PUFA metabolites are not only biomarkers of lipid peroxidation but also mediators of oxidant injury, and especially the NeuroPs.

### 4.1 Neuroprostanes

It is well reported that an enriched n-3 PUFA diet confers cardioprotective effects due primarily to the two main PUFA, EPA and DHA (GISSI-Prevenzione Investigators, 1999). A large prospective study showed that the most marked effect of DHA and EPA supplementation is a reduction of sudden cardiac death in the months following a cardiac infarction. This benefit has been explained, in part, by a reduction in arrhythmias and systolic cardiac failure. The anti-arrhythmic effects of n-3 PUFA have been confirmed in animal models of cardiac infarction by ligation of the left coronary artery and reported in 2003 by Judé *et al.* (2003). These and other studies in single cardiac cells have shown that EPA and DHA can modulate the activity of ion channels, the transmembrane proteins responsible for the electrical activity of the heart. However, it has been suggested that oxygenated metabolites of EPA and DHA may also play a role in these actions. In this regard, it has been shown that some of the effect of DHA on rat cardiac ion channels was due to an oxygenated metabolite of DHA, the 4(RS)-4-F<sub>4t</sub>-NeuroP (Fig. 7) (Roy *et al.*, 2015).

Roy *et al.* (2015) have tested different F<sub>4</sub>-NeuroPs on arrhythmias induced by isoprenaline and stimulation frequency of isolated ventricular mice cardiac cells. Among them, some F<sub>4</sub>-NeuroPs have anti-arrhythmic effects (IC<sub>50</sub> ≈ 100 nM). The main metabolite, the 4(RS)-4-F<sub>4t</sub>-NeuroP, showed potent dose-dependent *in cellulo* and also *in vivo* in permanent myocardial infarction (PMI) mice. At the cellular level, the mechanism of action is unlikely to be due to a β-blocker effect, but the anti-arrhythmic property can instead be explained by a rycal-like effect; in particular, stabilization of the RyR2 complex with FKBP12.6 (Andersson and Marks, 2010; Roy *et al.*, 2017).

In 2017, Bosviel *et al.* (2017) reported that the 4(RS)-4-F<sub>4t</sub>-NeuroP and the 14-A<sub>4t</sub>-NeuroP possess an anti-inflammatory properties mediated by PPAR receptors, using primary microglial cells.

Lacampagne *et al.* (2022a, b) have tested first the 4(RS)-4-F<sub>4t</sub>-NeuroP on Ventilator Induced Diaphragm Dysfunction (VIDD) and confirmed that this metabolite permits to restore diaphragm muscular activity on VIDD mice and rat. This phenomenon is once again mediated again by RYR1 receptor. Later, Lacampagne *et al.* (2022a, b) validated the proof of concept on adult pig of the activities of 4(RS)-4-F<sub>4t</sub>-NeuroP and another compound on VIDD with a submicromolar inhibitory concentration and three patents were published (Le Guennec *et al.*, 2012; Lacampagne *et al.*, 2022a, b). (WO 2015197562 A1 20151230, EP12306519.3, EP22305460.2, EP22209466.6).

In 2020, Lee *et al.* (2020) reported for the first time that native 4(RS)-4-F<sub>4t</sub>-NeuroP has a regulatory role in neurons for cell survival on human SH-SY5Y neuroblastoma cells.

Geng *et al.* (2022) have also reported a neuroprotective effect of 4(RS)-4-F<sub>4t</sub>-NeuroP on primary mouse microglial and BV2 cells and that the 4(RS)-4-F<sub>4t</sub>-NeuroP attenuate LPS-induced mitochondrial membrane potential loss in BV2 cells.

Finally, Moretti *et al.* (2023) reported this year that 4(RS)-4-F<sub>4t</sub>-NeuroP possess an effect on human sperm and precisely a role on sperm capacitation mediated again by a ryanodine receptor.

It should be mentioned that to date, there is no biological activity reported for the dihomio-IsoPs.

## 5 Conclusion

Our understanding of the role of PUFA peroxidation in the pathogenesis of various human diseases is at an early stage. Regarding DHA, we know that free radical-induced autoxidation of this PUFA occurs in numerous pathological conditions from cardiovascular disorders to cancers and neurodegenerative diseases. Through our knowledge in organic chemistry, we can contribute to clinical and basic research by developing novel synthetic approaches and providing samples for biological and analytical studies. Several new approaches for chiral synthesis of NeuroPs and others isoprostanooids such as dihomio-IsoPs are now available. Some of these products may be used as markers for the diagnosis and management of patients and will need to be measured accurately and precisely. The contribution of each of these unique NeuroPs to tissue and organ damage has to be clearly ascertained within a complex network of signalling molecules and mediators. Despite all the work performed in this field, there is still a lot to discover, and collaborations between chemists and biologists are in this sense highly important.

## Authors contribution

Camille Oger: Writing-original draft, preparation, validation. Valerie Bultel-Poncé: Methodology. Alexandre Guy: Methodology. Valérie Gros: Methodology. Guillaume Reversat: Methodology. Claire Vigor: Validation. Jean-Marie Galano: Validation. Thierry Durand: Supervision, writing-original draft, preparation, validation.

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## References

- Ahmed OS, Galano J-M, Pavlickova T, *et al.* 2020. Moving forward with isoprostanes, neuroprostanes and phytoprostanes—Where are we now? *Essays Biochem* 64: 463–484.
- Andersson DC, Marks AR. 2010. Fixing ryanodine receptor Ca<sup>2+</sup> leak—A novel therapeutic strategy for contractile failure in heart and skeletal muscle. *Drug Discov Today: Dis Mech* 7: e151–e157.
- Barden A, Beilin LJ, Ritchie J, Croft KD, Walters BN, Michael CA. 1996. Plasma and urinary 8 isoprostane as an indicator of lipid peroxidation in preeclampsia and normal pregnancy. *Clin Sci (Lond)* 91: 711–718.
- Barden AE, Mori TA, Dunstan JA, *et al.* 2004. Fish oil supplementation in pregnancy lowers F<sub>2</sub>-isoprostanes in neonates at high risk of atopy. *Free Radic Res* 38: 233–239.
- Barden AE, Corcoran TB, Mas E, *et al.* 2012. Are isofurans and neuroprostanes increased after aneurysmal subarachnoid hemorrhage and traumatic brain injury? *Antioxid Redox Signal* 16: 165–169.
- Bosviel R, Joumard-Cubizolles L, Chinetti-Gbaguidi G, *et al.* 2017. DHA-derived oxylipins, neuroprostanes and protectins, differentially and dose-dependently modulate the inflammatory response in human macrophages: Putative mechanisms through PPAR activation. *Free Radic Biol Med* 103: 146–154.
- Brinkmann Y, Oger C, Guy A, Durand T, Galano JM. 2010. Total synthesis of 15-D<sub>21</sub>- and 15-E<sub>21</sub>-isoprostanes. *J Org Chem* 75: 2411–2414.
- Cascant-Vilaplana MM, Sánchez-Illana Á, Piñeiro-Ramos JD, *et al.* 2021. Do levels of lipid peroxidation biomarkers reflect the degree of brain injury in newborns? *Antiox Redox Signal* 37: 1467–1475.
- Collado-Gonzales J, Medina S, Durand T, *et al.* 2015. New UPLC-QqQ-MS/MS method for quantitative and qualitative determination of 10 phytoprostanes in foodstuffs in commercial olive and sunflower oils. *Food Chem* 178: 212–220.
- Corcoran TB, Mas E, Barden AE, *et al.* 2011. Are isofurans and neuroprostanes increased after aneurysmal subarachnoid hemorrhage and traumatic brain injury? *Antioxid Redox Signal* 15: 2663–2667.
- Cortelazzo A, De Felice C, Guerranti R, *et al.* 2016. Abnormal N-glycosylation pattern of brain nucleotide pyrophosphatase-5 (NPP-5) in *Mecp2*-mutant murine models of Rett syndrome. *Neurosci Res* 105: 28–34.
- De Felice C, Signorini C, Durand T, *et al.* 2011. Dihomo-isoprostanes as potential early biomarkers of lipid oxidative damage in Rett syndrome 2011. *J Lipid Res* 52: 2287.
- De Felice C, Signorini C, Leoncini S, *et al.* 2012. The role of oxidative stress in Rett syndrome: An overview. *Ann NY Acad Sci* 1259: 121–135.
- De La Torre A, Lee YY, Oger C, *et al.* 2014. Synthesis, discovery and quantitation of dihomoprostanes: Novel biomarkers of *in vivo* adrenergic acid peroxidation. *Angew Chem Int Ed* 53: 6249–6252.
- De La Torre A, Lee YY, Mazzoni A, *et al.* 2015. Total syntheses and *in vivo* quantitation of novel neurofuran and dihomoprostane derived from docosahexaenoic acid and adrenergic acid. *Chem Eur J* 21: 2442–2446.
- Dupuy A, Le Faouder P, Vigor C, *et al.* 2016. Simultaneous quantitative profiling of 20 isoprostanes from omega-3 and omega-6 polyunsaturated fatty acids by LC-MS/MS in various biological samples. *Anal Chim Acta* 921: 46–58.
- Farias SE, Basselin M, Chang L, Heidenreich KA, Rapoport SI, Murphy RC. 2008. Formation of eicosanoids, E<sub>2</sub>/D<sub>2</sub> isoprostanes, and docosanoids following decapitation-induced ischemia, measured in high-energy-microwaved rat brain. *J Lipid Res* 49: 1990–2000.
- Fessel JP, Porter NA, Moore KP, Sheller JR, Roberts-II LJ. 2002. Discovery of lipid peroxidation products formed *in vivo* with a substituted tetrahydrofuran ring (isofurans) that are favored by increased oxygen tension. *Proc Natl Acad Sci USA* 99: 16713–16718.
- Galano J-M, Mas E, Barden A, *et al.* 2013. Isoprostanes and neuroprostanes: Total synthesis, biological activity and biomarkers of oxidative stress in humans. *Prostagl Other Lipid Med* 107: 95–102.
- Galano J-M, Lee JC-Y, Gladine C, *et al.* 2015. Non-enzymatic cyclic oxygenated metabolites of adrenergic, docosahexaenoic, eicosapentaenoic,  $\alpha$ -linolenic acids; bioactivities and potential use as biomarkers. *Biochim Biophys Acta* 1851: 446–455.
- Galano J-M, Lee YY, Oger C, *et al.* 2017. Isoprostanes, neuroprostanes, phytoprostanes. An overview of 25 years of research in chemistry and biology. *Prog Lipid Res* 68: 83–108.
- Garcia-Blanco A, Pena-Bautista C, Oger C, *et al.* 2018. Reliable analytical method to determine new lipid peroxidation biomarkers in urine samples: Application to mild cognitive impairment due to Alzheimer disease. *Talanta* 184: 193–201.
- Geng X, Galano J-M, Oger C, Sun GY, Durand T, Lee JC. 2022. Neuroprotective effects of DHA-derived peroxidation product 4(RS)-4-F<sub>4t</sub>-neuroprostane on microglia. *Free Radic Biol Med* 185: 1–5.
- GISSI-Prevenzione Investigators. 1999. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: Results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* 354: 447.
- Gladine C, Newman JW, Durand T, *et al.* 2014. Lipid profiling following intake of omega 3 fatty acid DHA identifies the peroxidized metabolites DHA F<sub>4t</sub>-neuroprostanes as the best predictors of atherosclerosis prevention. *PLoS ONE* 9: e89393.
- Guy A, Oger C, Heppkeausen J, *et al.* 2014. Oxygenated metabolites of n-3 polyunsaturated fatty acid as potential oxidative stress biomarkers: Total synthesis of 8-F<sub>3t</sub>-IsoP, 10-F<sub>4t</sub>-NeuroP, and [D<sub>4</sub>]-10-F<sub>4t</sub>-NeuroP. *Chem Eur J* 20: 6374–6380.
- Hsieh YP, Lin CL, Shiue AL, *et al.* 2009. Correlation of F<sub>4t</sub>-neuroprostanes levels in cerebrospinal fluid with outcome of aneurysmal subarachnoid hemorrhage in humans. *Free Radic Biol Med* 47: 814–824.
- Imbusch R, Mueller MJ. 2000. Formation of isoprostane F<sub>2</sub>-like compounds (phytoprostanes F<sub>1</sub>) from  $\alpha$ -linolenic acid in plants. *Free Radical Biol Med* 28: 720–726.
- Jahn U, Galano JM, Durand T. 2008. Beyond prostaglandins chemistry and biology of cyclic oxygenated metabolites formed by free-radical pathways from polyunsaturated fatty acids. *Angew Chem Int Ed* 47: 5894–5951.
- Judé S, Bedut S, Roger S, *et al.* 2003. Peroxidation of docosahexaenoic acid is responsible for its effects on ITO and ISS in rat ventricular myocytes. *Br J Pharmacol* 139: 816.
- Lacampagne A, Galano J-M, Oger C, *et al.* *Eur Patent* (05 April 2022, EP22305460. 2).
- Lacampagne A, Galano J-M, Oger C, *et al.* *Eur Patent* (22 November 2022, EP22209466. 6).
- Lee YY, Galano J-M, Oger C, *et al.* 2016. *Lipids* 51: 1217–1229.
- Lee YY, Galano J-M, Leung HH, *et al.* 2020. Non-enzymatic oxygenated metabolite of docosahexaenoic acid, 4(RS)-4-F<sub>4t</sub>-neuroprostane, act as bioactive lipid molecule in neuronal cell 2020. *FEBS Lett* 594: 1797–1808.



- Le Guennec J-Y, Galano JM, Oger C, *et al.* *Eur Patent* (5 December 2012, EP12306519. 3).
- Mas E, Michel F, Guy A, *et al.* 2008. Quantification of urinary F<sub>2</sub>-isoprostanes with 4(RS)-F<sub>4t</sub>-neuroprostane as an internal standard using gas-chromatography mass spectrometry: Application to polytraumatized patients. *J Chromatogr B* 10: 5087–5090.
- Michel F, Bonnefont-Rousselot D, Mas E, Draï J, Thérond P. 2008. Biomarkers of lipid peroxidation: Analytical aspects. *Ann Biol Clin* 66: 605.
- Milne GL, Yin H, Brooks JD, Sanchez S, Roberts II LJ, Morrow JD. 2007. Quantification of F<sub>2</sub>-isoprostanes in biological fluids and tissues as a measure of oxidant stress. *Methods Enzymol* 433: 113–126.
- Moretti E, Signorini C, Noto D, *et al.* 2023. F<sub>4</sub>-neuroprostanes effects on human sperm 2023. *Int J Mol Sci* 24: 935.
- Morrow JD, Hill KE, Burk RF, Nammour TM, Badr KF, Roberts II LJA. 1990. A series of prostaglandin F<sub>2</sub>-like compounds are produced *in vivo* in humans by a non-cyclooxygenase, free radical-catalyzed mechanism. *Proc Natl Acad Sci USA* 87: 9383–9387.
- Nourooz-Zadeh J, Liu EH, Anggard E, Halliwell B. 1998. F<sub>4</sub>-isoprostanes: A novel class of prostanoids formed during peroxidation of docosahexaenoic acid (DHA). *Biochem Biophys Res Commun* 242: 338.
- Oger C, Brinkmann Y, Bouazzaoui S, Durand T, Galano J-M. 2008. Stereocontrolled access to isoprostanes *via* a bicyclo[3.3.0]octene framework. *Org Lett* 10: 5087–5090.
- Oger C, Marton Z, Brinkmann Y, *et al.* 2010a. New insight in lipase-catalyzed regioselective monoacetylation of unsymmetrical 1,5-primary diols. *J Org Chem* 75: 1892–1897.
- Oger C, Bultel-Poncé V, Guy A, *et al.* 2010b. The handy use of Brown's catalyst for a skipped diyne deuteration: Application to the synthesis of a d<sub>4</sub>-labeled-F<sub>4t</sub>-neuroprostane. *Chem Eur J* 16: 13976–13980.
- Oger C, Bultel-Poncé V, Guy A, Durand T, Galano J-M. 2012. Total synthesis of isoprostanes derived from AdA and EPA. *Eur J Org Chem* 2012: 2621–2634.
- Peña-Bautista C, Vigor C, Galano J-M, *et al.* 2019. New screening approach for Alzheimer's disease risk assessment from urine lipid peroxidation compounds. *Sci Rep* 9: 14244.
- Roberts II LJ, Montine TJ, Markesbery WR, *et al.* 1998. Formation of isoprostane-like compounds (neuroprostanes) *in vivo* from docosahexaenoic acid. *J Biol Chem* 273: 13605–13612.
- Roy J, Oger C, Thireau J, *et al.* 2015. Nonenzymatic lipid mediators neuroprostanes exert the anti-arrhythmic properties of docosahexaenoic acid. *Free Radic Biol Med* 86: 269–278.
- Roy J, Fauconnier J, Oger C, *et al.* 2017. Non-enzymatic oxidized metabolite of DHA, 4(RS)-4-F<sub>4t</sub> neuroprostane protects the heart against reperfusion injuries. *Free Radic Biol Med* 102: 229–239.
- Rund KM, Ostermann AI, Kutzner L, *et al.* 2018. Development of an LC-(ESI)-MS/MS method for the simultaneous quantification of 35 isoprostanes and isofurans derived from the major n3 and n6 PUFA. *Anal Chim Acta* 1037: 63–74.
- Sánchez-Illana Á, Thayyil S, Montaldo P, *et al.* 2017. Novel free-radical mediated lipid peroxidation biomarkers in newborn plasma. *Anal Chim Acta* 996: 88–97.
- Signorini C, De Felice C, Durand T, *et al.* 2018. Relevance of 4-F<sub>4t</sub>-neuroprostane and 10-F<sub>4t</sub>-neuroprostane to neurological diseases. *Free Radic Biol Med* 115: 278–287.
- Signorini C, Cardile V, Pannuzzo G, *et al.* 2019. Increased isoprostanoid levels in brain from murine model of Krabbe disease – Relevance of isoprostanes, dihom-isoprostanes and neuroprostanes to disease severity. *Free Radic Biol Med* 139: 46–54.
- Signorini C, Moretti E, Noto D, *et al.* 2021. F<sub>4</sub>-neuroprostanes: A role in sperm capacitation. *Life* 11: 655.
- Signorini C, De Felice C, Durand T, *et al.* 2022. Isoprostanoid plasma levels are relevant to cerebral adrenoleukodystrophy disease. *Life* 12: 146.
- Stafforini DM, Sheller JR, Blackwell TS, *et al.* 2006. Release of free F<sub>2</sub>-isoprostanes from esterified phospholipids is catalyzed by intracellular and plasma platelet-activating factor acetylhydrolases. *J Biol Chem* 281: 4616–4623.
- Song W-L, Lawson JA, Reilly D, *et al.* 2008. Neurofurans, novel indices of oxidant stress derived from docosahexaenoic acid. *J Biol Chem* 283: 6–16.
- VanRollins M, Woltjer RL, Yin H, Morrow JD, Montine TJ. 2008. F<sub>2</sub>-dihomo-isoprostanes arise from free radical attack on adrenic acid. *J Lipid Res* 49: 995.
- Vigor C, Bertrand-Michel J, Pinot E, *et al.* 2014. Non-enzymatic lipid oxidation products in biological systems: Assessment of the metabolites from polyunsaturated fatty acids. *J Chromatogr B* 964: 65–78.
- Vigor C, Balas L, Guy A, *et al.* 2022. Isoprostanoids, isofuranoids and isoketals – From synthesis to lipidomics. *Eur J Org Chem* 22: e202101523.

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