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Characterization and modulation of brain lipids content of rainbow trout fed with 100% plant based diet rich in omega-3 long chain polyunsaturated fatty acids DHA and EPA

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ABSTRACT

Brain functions are known to be mainly modulated by adequate dietary intake. Inadequate intake as can be an excess or significant deficiency affect cognitive processes, behavior, neuroendocrine functions and synaptic plasticity with protective or harmful effects on neuronal physiology. Lipids, in particular, ω-6 and ω-3 long chain polyunsaturated fatty acids (LC-PUFAs) play structural roles and govern the different functions of the brain. Hence, the goal of this study was to characterize the whole brain fatty acid composition (precursors, enzymatic and non-enzymatic oxidation metabolites) of fish model of rainbow trout fed with three experimental plant-based diet containing distinct levels of eicosapentaenoic acid (EPA, 20:5 ω-3) and docosahexaenoic acid (DHA, 22:6 ω-3) (0% for low, 15.7% for medium and 33.4% for high, total fatty acid content) during nine weeks. Trout fed with the diet devoid of DHA and EPA showed reduced brain content of total ω-3 LC-PUFAs, with diminution of EPA and DHA. Selected enzymatic (cyclooxygenases and lipoxygenases) oxidation metabolites of arachidonic acid (AA, 20:4 ω-6) decrease in medium and high ω-3 LC-PUFAs diets. On the contrary, total selected enzymatic oxidation metabolites of DHA and EPA increased in high ω-3 LC-PUFAs diet. Total selected non-enzymatic oxidation metabolites of DHA (not detected for EPA) increased in medium and high ω-3 LC-PUFAs diets. In conclusion, this work revealed for the first time in fish model the presence of some selected enzymatic and non-enzymatic oxidation metabolites in brain and the modulation of brain lipid content by dietary DHA and EPA levels.
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1. Introduction

In the modulation of brain function, food sensing represents the first step which finally orchestrate by several nutrients-sensors a wide range of biological functions and processes, including feeding behavior, mainly through neuroendocrine mechanisms and autonomic terminals [1]. Among these nutrients sensors, foods contain different types of fatty acids (FA) that are either saturated or mono/polyunsaturated. Their impact on health strongly depends on fat types and daily fat intake. In this respect, the main ω-6, AA and ω-3 LC-PUFAs, DHA which are nutrients widely present among dietary lipids. Over the last year, adequate dietary lipids have garnered recognition for their direct actions on brain functions and activity [2,3] and also including neurogenesis, the regulation and resolution of inflammation and membrane fluidity [3]. However, in mammals, the synthesize capacity of LC-PUFAs by brain is limited [4], they have to be directly provided through the diet. Hence, increased consumption of fish oil (rich in ω-3 LC-PUFAs) results in a partial replacement of AA by ω-3 LC-PUFAs (EPA and DHA) in cellular membranes [5] whereas lower dietary ω-3 LC-PUFAs intake leads to decreased DHA brain content in rodents [6] and monkeys [7] and unchanged ones in rats [8], while it leads to increased AA brain levels in monkeys [7] and rodents [9] and again, comparable ones in

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mice [10] and rats [8].

LC-PUFAs presents among dietary lipids have different properties. In fact, more than their precursor, the specific enzymatic oxidation metabolites of LC-PUFAs have garnered recognition for their direct actions on brain [11]. Indeed, through several enzymatic reactions (cyclooxygenase-1 and 2, 5-lipoxygenase, 15-lipoxygenase, 12/15-lipoxygenase or cytochrome P450 pathways), AA is a precursor of eicosanoids (*i.e.* prostaglandins), thromboxanes and leukotrienes known as pro-inflammatory mediators [12]. In contrast, ω-3 LC-PUFAs are converted to enzymatic metabolites known to be present and bioactive in the brain [11]. Among them, resolvins and protectins are known to be anti-inflammatory mediators and having pro-resolving properties [13]. Conversely, due to several double bonds in their structures, LC-PUFAs are very sensitive to non-enzymatic peroxidation leading to the formation of stable oxidized metabolites like F_2-isoprostanes from AA [14], phytoprostanes from alpha linolenic acid (ALA), F_3-isoprostanes from EPA and F_4-neuroprostanes from DHA [15]. Oxidized metabolites have been shown to be biologically active mediators [16] of oxidant injury. In many species and vascular beds, they are vasoconstrictors [17]. They modulate platelet activity [18] and monocyte adhesion [19], induce proliferation of endothelial and smooth muscle cells [20], as well as anti-proliferation of cancer cells [21], and exert cardioprotective effects [22,23]. However, in mammals, participation of non-enzymatic oxidation metabolites in brain functions remains poorly documented.

In fish, to cope of growing booming of aquaculture and to fit with environmental and ecological impacts, social and economic sustainability of the aquaculture, the traditional majors ingredients of aquafeed [24], fishmeal (FM) and fish oil (FO), rich in ω-3 LC-PUFAs, DHA and EPA, must be replaced by renewable and alternative sources like terrestrial plants products. However, after twenty years of research [25], in addition to a drastic alteration of fish growth performance and survival rate [26,27], the total replacement of marine products with plant products led to an unfavorable modification of the fatty-acid composition of farmed fishes [28], particularly of the EPA and DHA. Indeed, modern and sustainable aquafeeds contain increasing levels of terrestrial agriculture alternatives like plant based-diet totally devoid of LC-PUFAs. This has resulted in a substantial drop in EPA and DHA level until 50% in the flesh of farmed fishes [29]. At brain level, some studies revealed that fatty acid in the diet of farmed fish impacted their feeding behavior [30–32] involving a neuropeptide pathway (*via* change in the expression of anorexigenic and orexigenic neuropeptides) [30,32–34], modulation of membrane biophysical properties (increased number of receptors) [35], up- or down-regulation of neurotransmitter release [36], or augmentation of cerebral blood flow in response to stimulation (modulation of neuronal excitability) [37]. However, the impact of dietary ω-3 LC-PUFAs (EPA and DHA) on brain total lipid content of rainbow trout and their enzymatic and non-enzymatic oxidation metabolites on brain fatty acid composition have never been investigated. Moreover, to characterize the fatty acid composition at brain trout level will then be able to focus on their effects on brain functions that can modulate feed intake and growth performance.

While numerous mammals' models of LC-PUFAs modulation are reported in the literature (effects of aging, genetic model, dietary approaches), brain LC-PUFAs composition with fish models is missed. Hence, the aim of this present study was to characterize the whole brain fatty acid content and modulation (precursors, enzymatic and non-enzymatic oxidation metabolites) in rainbow trout fed with three experimental plant based-diets containing distinct levels of ω-3 LC-PUFAs (EPA and DHA).

2. Materials and methods

2.1. Ethics statement

The experiment was performed in accordance with EU legal frameworks relating to the protection of animals used for scientific purposes (*i.e.* Directive 2010/63/EU) and following the Guidelines of the National Legislation on Animal Care of the French Ministry of Research (Decree No 2013–118, dated February 1, 2013). After approval by the ethical committee (C2EA-73) of INRA "Comité d'éthique Aquitain poissons oiseaux" (N° agreement INRA 19869, 28 June 2019), the experiment was conducted at the experimental facilities at Donzacq (permit number A40–228.1, Landes, France).

2.2. Experimental diets

Using a twinscrew extruder (Clextral), diets (pellets of 3 mm diameter and length) were manufactured at the INRA experimental facilities in Donzacq. Formulation and proximate analysis of diets are presented in Table 1. All the diets were completely free from FM and FO and formulated with the same feed ingredients, they differ only in their oil composition. In order to avoid exceeding anti-nutrient threshold levels, we used different protein sources (*c.* 41.74% of total diet), a blend of wheat gluten, rapeseed meal, whole wheat, corn gluten meal, extruded peas, and white lupin. To correct the deficiency in essential amino acids, synthetic L-lysine, L-methionine, phosphorous and phospholipids, dicalciumphosphate and soy-lecithin were added to all diets. Diets were cover the nutrient requirements of rainbow trout [38] and were isoenergetic (*c.* 24.5 kJg^{-1} of dry diet). To maintain a constant ratio between groups of different fatty acids (saturated, monounsaturated, ω-3, ω-6, and ω-9 PUFA), the diets differed mainly by the level of DHA and EPA to the expense of ALA which were brought by adding Omegavie® marine oils DHA and EPA (Polaris functional lipids, Quimper, France) in two diets (medium and high ω-3 LC-PUFAs diet). The three experimental diets contained 23.7% crude lipids with 0.0% of ω-3 DHA/EPA (% of total fatty acids) for low ω-3 LC-PUFAs, 15.7% for medium ω-3 LC-PUFAs (7.6% of EPA and 8.1% of DHA) and 33.5% for high ω-3 LC-PUFAs diets (15.8% of EPA and 17.7% of DHA). The fatty acid composition of the diets is shown in Table 2.

The nutrient composition of diets (protein and lipid content, gross energy, ash and starch content) was extracted, determined and analysed as previously described [39].

2.3. Fish and experimental design

Female rainbow trout used in this present study originated from the same parental stock (INRA Fish Farm of Lees-Athas, Permit number A64.104.1, vallée d'Aspe, France). Fish were reared at 18 °C in the INRA experimental facilities at Donzacq, Landes, France as previously described [39]. Juveniles trout (60.70 ± 0.4 g) (Table 3) were randomly distributed into nine tanks at the density of 25 fish/tank. Fish were reared in triplicates and fed by hand twice a day with an interval 8 h, until apparent satiety during 9 weeks with the three experimental diet.

At the end of 9 weeks of feeding, fish were first anaesthetized (benzocaine, 30 mg l^{-1}) and then killed (benzocaine, 60 mg l^{-1}) 6 h after the last meal. Two brain per tank (six brain per condition) were dissected for each lipid analysis (six fish for total lipid analysis, six fish for non-enzymatic lipid mediator analysis and six fishes for enzymatic lipid mediator analysis). Brain tissues extracted were immediately frozen (liquid nitrogen), and stored at −80 °C for further analysis.

Table 1
Ingredients and composition of the ω-3 LC-PUFAs diets.

Ingredient (%)	DIET		
	LOW ω-3 LC-PUFAs	**MEDIUM ω-3 LC-PUFAs**	**HIGH ω-3 LC-PUFAs**
Extruded whole wheat	20.0	20.0	20.0
Corn gluten	16.0	16.0	16.0
Wheat gluten	13.0	13.0	13.0
Peas meal	10.0	10.0	10.0
Extruded Peas	8.0	8.0	8.0
White lupin seed meal	3.0	3.0	3.0
Rapeseed meal	4.0	4.0	4.0
Soy lecithin	2.0	2.0	2.0
L-Lysine	1.0	1.0	1.0
L-methionine	0.5	0.5	0.5
$CaHPO_4 \cdot 2H_2O$	0.5	0.5	0.5
Mineral premix[a]	1.5	1.5	1.5
Vitamin premix[b]	1.5	1.5	1.5
Attractant mix[c]	1.5	1.5	1.5
Palm oil	1.5	2.0	1.1
Sunflower oil	3.5	4.15	3.1
Rapeseed oil	3.0	3.9	2.7
Linseed oil	9.5	2.9	1.0
Omegavie® DHA marine oil (min 70%)[d]	0.0	2.6	5.6
Omegavie® EPA marine oil (min 70%)[e]	0.0	1.95	4.0
Composition (% of dry matter)			
Dry matter (in % of diet)	96.73	96.9	96.87
Crude protein	42.62	41.52	41.1
Crude lipid	23.66	23.75	23.7
Starch	14.92	15.21	14.96
Ash	4.37	4.39	4.27
Energy (kJg-1 DM)	24.51	24.62	24.47

[a] Mineral premix: (g or mg kg^{-1} diet): calcium carbonate (40% Ca), 2.15 g; magnesium oxide (60% Mg), 1.24 g; ferric citrate, 0.2 g; potassium iodide (75% I), 0.4 mg; zinc sulphate (36% Zn), 0.4 g; copper sulphate (25% Cu), 0.3 g; manganese sulphate (33% Mn), 0.3 g; dibasic calcium phosphate (20% Ca, 18% P), 5 g; cobalt sulphate, 2 mg; sodium selenite (30% Se), 3 mg; KCl, 0.9 g; NaCl, 0.4 g (UPAE, INRA).
[b] Vitamin premix: (IU or mg kg^{-1} diet): DL-a tocopherol acetate, 60 IU; sodium menadione bisulphate, 5 mg; retinyl acetate, 15,000 IU; DL-cholecalciferol, 3000 IU; thiamin, 15 mg; riboflavin, 30 mg; pyridoxine, 15 mg; B12, 0.05 mg; nicotinic acid, 175 mg; folic acid, 500 mg; inositol, 1000 mg; biotin, 2.5 mg; calcium pantothenate, 50 mg; choline chloride, 2000 mg (UPAE, INRA).
[c] Attractant mix: glucosamine, 0.5 g; taurine, 0.3 g; betaine, 0.3 g; glycine, 0.2 g; alanine, 0.2 g.
[d] Omegavie® DHA oil (min 70%): concentrated marine oil produced mainly from anchovy and sardine oil. The crude oil is first refined, then purified and concentrated. This oil contains marine DHA Omega 3 fatty acids under Triglycerides form. From Polaris, Quimper, France.
[e] Omegavie® EPA oil (min 75%): concentrated marine oil produced mainly from anchovy and sardine oil. The crude oil is first refined, then purified and concentrated. This oil contains marine EPA Omega 3 fatty acids under Triglycerides form. From Polaris, Quimper, France.

2.4. Variables and analysis

At the beginning and at the end of the trial juvenile trout were counted and weighed as a group. Variables related to growth were final body weight (FBW), body weight gain (FBW minus initial body weight, IBW), daily growth coefficient (DGC, 100 x (FBW0.33−IBW0.33)/days, % per day) and feed efficiency (FBW/food intake, FI). Variables related to FI were expressed in relative terms (% BW/day). Daily digestive energy intake (DEI) was obtained by multiplying FI by the digestible energy (DE content) of the diet (estimated as 23.07 kJg^{-1}). Variables related to zootechnical parameters are presented in Table 3.

2.5. Lipids analysis

Total lipids of whole brain tissues (Table 4) were extracted as previously published [40] and Fatty acid methyl esters were prepared (from fish lipid extracts) according to Shantha & Ackman [41] and analysed as previously published [42]. For extraction of enzymatic lipid mediators (Table 5), preparation for quantification of enzymatic lipid mediators were used as previously published [43]. LC-MS/MS analyses of oxylipins were performed as described [44]. Data were acquired in Multiple Reaction Monitoring (MRM) mode with optimized conditions (ion optics and collision energy). Peak detection, integration and quantitative analysis were done using Mass Hunter Quantitative analysis software (Agilent Technologies) based on calibration lines built with commercially available oxylipins standards (Cayman Chemicals). After having carried out a suitable extraction of the lipids, levels of non-enzymatic lipid mediators [45–48] (Table 6) were measured in fish brain by micro-LC-MS/MS as previously described [49]. Concentration of the non-enzymatic lipid mediators was obtained by calibration curves calculated by the area ratio of analytes and IS. Data processing was achieved using the MultiQuant 3.0 software (Sciex Applied Biosystems).

2.6. Statistical analysis

To assess the differences between diets and interactions, data were analysed by two-way ANOVA followed by Post-hoc Tukey test to compare all the groups if interactions between diets and lines were statistically significant. All data are expressed as mean ± S.E. Diets interaction were considered statistically significant at $P < 0.05$. When P values is inferior to $P < 0.001$, we mentioned $P < 0.00$. R software (v3.5.2)/R Commander package were used for all statistical analyses. Analyses were carried out on untransformed raw data since criteria for normality (Shapiro-Wilk's test) and homogeneity of variances (Levene's test) were fulfilled.

Table 2
Selected fatty acid composition (% total fatty acids).

Ingredient (%)	Diet		
	LOW ω-3 LC-PUFAs	MEDIUM ω-3 LC-PUFAs	HIGH ω-3 LC-PUFAs
C14:0	0.2	0.2	0.1
C15:0	0.0	0.0	0.0
C16:0	9.7	9.4	6.7
C18:0	3.1	2.6	2.2
C20:0	0.3	0.3	0.4
Sum saturates	**13.7**	**13.2**	**9.9**
C16:1 ω-7	0.2	0.2	0.2
C18:1 ω-9	30.3	29.5	21.9
C20:1 ω-9	0.4	0.8	1.2
C22:1 ω-9	0.0	0.1	0.3
Sum monoenes	**30.9**	**30.7**	**23.7**
C18:2 ω-6	27.2	25.6	20.3
C18:3 ω-6	0.0	0.0	0.1
C20:2 ω-6	0.0	0.1	0.2
C20:3 ω-6	0.0	0.1	0.2
C20:4 ω-6	0.0	0.6	1.2
Sum ω-6 PUFAs	**27.4**	**26.5**	**22.0**
C18:3 ω-3	26.8	11.0	5.1
C18:4 ω-3	0.0	0.1	0.1
C20:3 ω-3	0.0	0.0	0.1
C20:4 ω-3	0.0	0.3	0.6
C20:5 ω-3	0.0	7.6	15.8
C22:5 ω-3	0.0	0.5	1.0
C22:6 ω-3	0.0	8.1	17.7
Sum ω-3 PUFAs	**26.9**	**27.6**	**40.3**
Sum ω-3 LC-PUFAs (EPA + DHA)	***0.0***	***15.7***	***33.4***
ω-3 (EPA + DHA)/ω-6	***0.0***	***0.6***	***1.5***

Table 3
Growth performance, feed utilization and whole body composition over the whole experimental period (9 weeks).

	Dietary treatment	**MEDIUM ω-3 LC-PUFAs**	**HIGH ω-3 LC-PUFAs**	One-way ANOVA (*p-values*)
	LOW ω-3 LC-PUFAs			Diet interaction
Final body weight (g per ind)	197.9 ± 6.28	200.34 ± 2.57	195.52 ± 2.92	0.73
Body weight gain (g per ind)	133.86 ± 5.75	139.11 ± 3.67	134.53 ± 2.74	0.73
Daily Growth Coefficient (% per day)	2.2 ± 0.09	2.25 ± 0.14	2.26 ± 0.03	0.73
Daily feed intake (% BW/day)	1.31 ± 0.02^{a}	1.30 ± 0.01^{ab}	1.25 ± 0.02^{b}	0.11
Feed efficiency (BWG/FI)	0.84 ± 0.01	0.85 ± 0.00	0.87 ± 0.03	0.11
Daily Digestive energy intake (KJ kg^{-1} BW)	778.3 ± 14.03	782.4 ± 4.09	758.3 ± 13.75	0.19
Total ω-3 feed (mg per ind per day)	0.0 ± 0.0^{c}	96.9 ± 4.38^{b}	194.0 ± 4.22^{a}	0.02
Composition (% of dry matter)				
Dry matter (%)	98.66	100.00	100.00	
Crude lipid	53.31 ± 0.39^{b}	55.54 ± 0.48^{a}	49.47 ± 0.55^{c}	0.00
Crude protein	44.55 ± 0.36	43.86 ± 0.39	45.58 ± 0.47	0.49
Ash	5.39 ± 0.08	5.13 ± 0.03	5.31 ± 0.03	0.07
Gross energy (kJ kg^{-1} of DM)	30.48 ± 0.08^{a}	30.75 ± 0.03^{a}	30.1 ± 0.1^{b}	0.00

Data are presented as mean ± SEM. *p-values* were produced by one-way ANOVA followed by Tukey's HSD comparison test.
Mean values that do not share a common letter are significantly different ($p < 0,05$). N = 3 tanks per diet.

3. Results

3.1. Fish performance

Growth and fish performance are presented in Table 3. After nine weeks, for all groups, fish tripled they body weight and very low mortalities were recorded (1 death). This represents a daily growth coefficient of 2.25 ± 0.05% of their initial body weight and no differences in body weight gain and final body weight were observed between the three LC-PUFAs diets. Concerning feed intake parameters, feed efficiency were not statistically different between the three groups whereas daily feed intake was lower for high *ω*-3 LC-PUFAs diet (1.31% BW/day for low *ω*-3 LC-PUFAs diet, 1.30% BW/day for medium *ω*-3 LC-PUFAs diet and 1.25% BW/day for high *ω*-3 LC-PUFAs diet, $p < 0.05$). Total *ω*-3 fatty acid intake was 96.9 mg per day for medium *ω*-3 diet and 194 mg per day for high*ω*-3 diet. Regarding body composition, crude protein and ash content were unaffected by the three LC-PUFAs diets whereas lipids and gross energy content was lower in fish fed the high *ω*-3 LC-PUFAs diet.

3.2. Proportions of fatty acids in whole brain

Total fatty acid proportions in whole brain are presented in Table 4 and Fig. 1 (% of total fatty acid). In whole brain content, the sum of saturates, monounsaturates and *ω*-6 PUFAs did not differ

Table 4
Total lipid whole brain content (% of fresh weight) and proportion (% of total fatty acid) of the main fatty acids.

Diets	LOW ω-3 LC-PUFAs		MEDIUM ω-3 LC-PUFAs		HIGH ω-3 LC-PUFAs		Diet interaction
	Mean	SEM	Mean	SEM	Mean	SEM	*p values*
Lipids (%)	6.36	0.39	5.94	0.36	6.01	0.16	*0.63*
C14:0	0.49	0.03	0.50	0.04	0.61	0.10	*0.39*
C15:0	0.09	0.03	0.09	0.04	0.06	0.01	*0.59*
C16:0	16.30	0.67	15.17	0.37	15.50	0.20	*0.27*
C17:0	0.06	0.00	0.06	0.01	0.07	0.00	*0.29*
C18:0	7.42	0.11	6.86	0.22	6.82	0.32	*0.07*
C20:0	0.16	0.06	0.37	0.19	0.18	0.05	*0.43*
C22:0	0.45	0.03	0.36	0.10	0.53	0.09	*0.56*
C24:0	0.24^{a}	0.02	0.24^{a}	0.04	0.18^{b}	0.01	*0.15*
Sum saturates	**25.22**	0.65	**23,67**	0.34	**23.96**	0.46	*0.25*
C16:1 ω-7	2.24	0.06	2.14	0.08	2.36	0.14	*0.43*
C18:1 ω-9	25.29	0.50	26.20	0.86	24.76	0.06	*0.56*
C20:1 ω-9	1.99^{b}	0.22	2.30^{ab}	0.13	2.48^{a}	0.05	*0.11*
C22:1 ω-9	0.30^{b}	0.06	0.40^{b}	0.02	0.53^{a}	0.03	***0.04***
Sum monoenes	**29.82**	0.64	**31.05**	0.92	**30.14**	0.19	*0.49*
C18:2 ω-6	3.87	0.29	5.67	1.08	3.81	0.54	*0.43*
C18:3 ω-6	0.15^{a}	0.02	0.11^{ab}	0.01	0.10^{b}	0.01	***0.01***
C20:2 ω-6	0.52^{a}	0.02	0.40^{b}	0.03	0.34^{c}	0.01	***0.04***
C20:3 ω-6	1.13^{a}	0.24	0.29^{b}	0.01	0.22^{c}	0.05	***0.03***
C20:4 ω-6	1.47	0.11	1.36	0.09	1.43	0.05	*0.56*
Sum ω-6 PUFA	**6.62**	0.24	**7.83**	1.03	**5.9**	0.59	*0.39*
C18:3 ω-3	1.71^{b}	0.22	1.31^{b}	0.23	0.76^{a}	0.15	*0.08*
C18:4 ω-3	0.30^{a}	4,00	0.22^{ab}	0.08	0.15^{b}	0.04	***0.04***
C20:3 ω-3	0.31^{a}	1,00	0.15^{b}	0.01	0.12^{b}	0.01	***0.04***
C20:4 ω-3	0.54^{a}	13,00	0.20^{b}	0.01	0.24^{b}	0.02	***0.04***
C20:5 ω-3	3.56^{b}	0.16	3.97^{b}	0.15	5.19^{a}	0.08	***0.04***
C22:5 ω-3	1.73	0.05	1.66	0.06	2.01	0.06	*0,06*
C22:6 ω-3	21.28^{b}	0.14	21.15^{ab}	0.91	22.42^{a}	0.51	*0.19*
Sum ω-3 PUFA	**29.43^{b}**	0.29	**28.64^{b}**	0.89	**30.89^{a}**	0.49	*0.06*
Sum ω-3 PUFA (EPA + DHA)	**24.84^{b}**	0.25	**25.11^{b}**	1.05	**27.62^{a}**	0.46	*0.06*
ω-3 (EPA + DHA)/ω-6	**3.31^{b}**	0.12	**3.14^{ab}**	0.57	**4.31^{a}**	0.38	*0.11*

Data are presented as mean ± SEM. *p-values* were produced by one-way ANOVA followed by Tukey's HSDcomparison test.
Mean values that do not share a common letter are significantly different ($p < 0{,}05$).

between the three diets (Fig. 1A). In fish fed the high ω-3 LC-PUFAs diet, Lignoceric acid (C24:0) for saturated fatty acids decreased whereas for monounsaturated fatty acids, Paullinic acid (C20:1) and Erucic acid (C22:1) increased (Table 4). Gamma-Linolenic acid (GLA, C18:3 ω-6) for ω-6 polyunsaturated fatty acid decreased with the high ω-3 LC-PUFAs diet, and Eicosadienoic acid (C20:2) and Dihomo-gamma-linolenic acid (DGLA, C20:3 ω-3) decreased with medium and high ω-3 experimental diets. The sum of ω-3 PUFAs and the ratio ω-3/ω-6 increased in fish fed the high ω-3 diet (Fig. 1A). ALA and Stearidonic acid (SDA, C18:4 ω-3) decreased with the high ω-3 diet and Eicosatrienoic acid (C20:3) and AA decreased with medium and high ω-3 diets. EPA and DHA were higher in fish fed the high ω-3 diet (Fig. 1B).

3.3. Selected enzymatic metabolites of fatty acids in whole brain

Selected enzymatic metabolites of fatty acids are presented in Table 5 and Fig. 2A for enzymatic metabolites of LA, AA, DHA and EPA. For enzymatic metabolites of AA from cyclooxygenase, PGE2 decreased in fish fed the high ω-3 LC-PUFAs diet. For enzymatic metabolites of AA from lipoxygenase, 12-HETE decreased with the medium and high ω-3 LC-PUFAs diet. No significant changes occurred in the other enzymatic metabolites of AA from cytochrome P450 and for enzymatic metabolites of AA (Fig. 2A). For enzymatic metabolites of LA (9 and 13-HODE from lipoxygenase) no significant changes have been observed as for total selected enzymatic metabolites of LA (Fig. 2A) between the three groups. For each enzymatic metabolites of EPA and DHA, no significant changes were observed from the three-enzymatic pathways (Table 5). However, total selected enzymatic metabolites from EPA and DHA increased in high ω-3 LC-PUFAs diet (Fig. 2A).

3.4. Selected non-enzymatic metabolites of fatty acid in whole brain

Selected non-enzymatic metabolites of fatty acid composition are presented in Table 6 and Fig. 2B for total selected non-enzymatic metabolites of ALA, DHA (EPA not detected). For non-enzymatic metabolites of ALA, phytoprostanes (PhytoP); ent-16-B$_{1t}$-PhytoP decreased in fish fed medium and high ω-3 LC-PUFAs diet. For non-enzymatic metabolites of DHA, neuroprostanes; 4(*RS*)-4-F$_{4t}$-NeuroP, 10(*R*)- and 10(*S*)-F$_{4t}$-NeuroP, 13A(*RS*)- and 13B(*RS*)-13-F$_{4t}$-NeuroP, 20(*R*)- and 20(*S*)-20-F$_{4t}$-NeuroP increased in brain with medium and high ω-3 LC-PUFAs diet (Table 6). Total selected non-enzymatic metabolites from DHA increased with medium and high ω-3 LC-PUFAs diet (Fig. 2B).

4. Discussion

The present work sought evidence to determine whether the fatty acid composition of brain of rainbow trout (precursors, enzymatic and non-enzymatic oxidation metabolites), are modulated or not, after nine week of feeding with experimental plant based-diets containing distinct levels of ω-3 LC-PUFAs (0% EPA/DHA for low ω-3 LC-PUFAs, 15.7% EPA/DHA for medium ω-3 LC-PUFAs and 33.4% EPA/DHA for high ω-3 LC-PUFAs, % total fatty acids). The importance of this study was to reveal for the first time the influence of ω-3 LC-PUFAs diet supplementation on fatty acid modulation at brain trout level. Knowing the major importance of the brain in regulating food intake, this study was the first step which enable to understand the alteration of growth performance of trout fed with 100% plant based-diet devoid of ω-3 LC-PUFAs. In this way, recent study demonstrated a causal link between a

Table 5
Selected enzymatic lipid metabolites of brain composition (pg/mg).

Diets	LOW ω-3 LC-PUFAs		MEDIUM ω-3 LC-PUFAs		HIGH ω-3 LC-PUFAs		Diet interaction
	Mean	SEM	Mean	SEM	Mean	SEM	*p values*
6kPGF1a (COX AA)	0.43	0.43	n/a		n/a		
11B-PGF2a (COX AA)	n/a		n/a		n/a		
PGD2 (COX AA)	6.41	0.85	7.23	0.72	6.87	0.48	0.71
PGE2 (COX AA)	36.20a	4.04	37.26a	4.32	23.97b	1.64	0.02
PGF2a (COX AA)	12.42	1.54	12.10	1.71	10.28	1.07	0.55
RvE1 (COX EPA)	n/a		n/a		n/a		
9-HODE (LOX LA)	163.11	17.49	180.93	31.67	147.56	20.75	0.63
13-HODE (LOX LA)	380.97	39.70	451.25	82.51	412.48	59.11	0.73
5-HETE (LOX AA)	58.73	7.56	51.66	5.55	60.40	4.78	0.57
5oxoETE (LOX AA)	45.99	7.60	44.49	6.21	52.70	4.99	0.63
8-HETE (LOX AA)	32.06	2.65	27.25	1.57	26.55	1.60	0.13
12-HETE (LOX AA)	254.81[a]	14.78	207.28[b]	12.54	171.13[c]	13.08	**0.00**
15-HETE (LOX AA)	67.75	9.78	63.94	7.69	66.94	5.87	0.94
8isoPGA2 (LOX AA)	n/a		n/a		n/a		
LTB4 (LOX AA)	n/a		n/a		n/a		
LTB5 (LOX AA)	n/a		n/a		n/a		
LxA4 (LOX AA)	3.01	1.48	1.94	1.41	3.42	1.45	0.76
LXB4 (LOX AA)	n/a		n/a		n/a		
14-HDoHE (LOX DHA)	318.67	39.45	329.78	30.35	410.84	42.94	0.19
17-HDoHE (LOX DHA)	337.70	56.57	368.74	34.91	438.85	41.24	0.23
7MaR1 (LOX DHA)	n/a		n/a		n/a		
PDx (LOX DHA)	n/a		n/a		n/a		
RVD1 (LOX DHA)	n/a		n/a		n/a		
RvD2 (LOX DHA)	n/a		n/a		n/a		
RvD3 (LOX DHA)	n/a		n/a		n/a		
RvD5 (LOX DHA)	n/a		n/a		n/a		
PGE3 (LOX EPA/DHA)	8.81	1.73	8.88	1.35	11.42	1.47	0.23
5,6-DiHETE (LOX EPA)	n/a		n/a		n/a		
18-HEPE (LOX EPA)	211.72	30.70	213.00	26.94	258.40	25.95	0.40
15dPGJ2 (LOX EPA)	n/a		n/a		n/a		
TXB2 (LOX EPA)	n/a		n/a		n/a		
14,15-EET (CYP450 AA)	5.59	0.90	6.03	0.53	5.59	0.55	0.43
11,12-EET (CYP450 AA)	n/a		n/a		n/a		
8,9-EET (CYP450 AA)	7.642	3.01	8.07	2.39	7.33	2.79	0.66
5,6-EET (CYP450 AA)	12.53	1.57	11.06	0.96	12.49	1.17	0.55

Data are presented as mean ± SEM. *p-values* were produced by one-way ANOVA followed by Tukey's HSD comparison test. ($p < 0,05$).
Mean values that do not share a common letter are significantly different ($p < 0,05$). n = 8 whole fish brain.
COX: cyclooxygenases enzymes; LOX: lipoxygenases enzymes; CYP450: cytochromes P450 enzymes; AA: arachidonic acid.
EPA: eicosapentaenoic acid; DHA: docoxahexaenoic acid.

Table 6
Selected non-enzymatic lipid oxidation metabolites of brain composition (mg/g).

Diets	LOW ω-3 LC-PUFAs		MEDIUM ω-3 LC-PUFAs		HIGH ω-3 LC-PUFAs		Diet interaction
	Mean	SEM	Mean	SEM	Mean	SEM	*p values*
4(RS)-4-F4t-NeuroP	3198.80[c]	145.46	4660.98[a]	135.46	3952.54[b]	154.03	0.00
10R–F4t-NeuroP	969.75[b]	35.17	1357.78[a]	46.01	1352.46[a]	38.51	0.00
10S-F4t-NeuroP	615.22[b]	23.77	934.40[a]	33.04	921.21[a]	23.28	0.00
13A(RS)-13-F4t-NeuroP	1811.35[b]	68.24	2561.17[a]	80.89	2642.65[a]	110.79	0.00
13B(RS)-13-F4t-NeuroP	3183.16[c]	185.44	4602.72[a]	138.88	4085.16[b]	189.90	0.00
20(R)-20-F4t-NeuroP	782.89[b]	41.48	1103.91[a]	24.17	1032.05[a]	35.24	0.00
20(S)-20-F4t-NeuroP	985.6[c]	60.87	1594.98[a]	35.01	1338.18[b]	60.28	0.00
Ent-16B1t-PhytoP	120.37[a]	8.07	67.73[b]	6.69	78.56[b]	7.18	0.00

Data are presented as mean ± SEM. *p-values* were produced by one-way ANOVA followed by Tukey's HSD comparison test. ($p < 0,05$).
Mean values that do not share a common letter are significantly different ($p < 0,05$). n = 8 whole fish brain.

behavioral deficit and ω-3 LC-PUFAs decrease in a discrete brain cell population suggesting that lower ω-3 LC-PUFAs biostatus could participate in the etiology of reward-related symptoms and then could influence food-reward [50].

This study demonstrated that all juveniles reached the same final body weight, with no differences in growth parameters (Table 3). However, daily feed intake was lower in fish fed high ω-3 LC-PUFAs diet than in fish fed low ω-3 LC-PUFAs diet (devoid of EPA/DHA). This result was in opposite to compared to our previous finding [42], this result was in opposite which revealed that fish preferred and consumed diet containing higher level of ω-3 LC-PUFAs diet. This difference may be due to the experimental methods implemented in these two studies. Using self-feeder materials in our previous study [42], the fishes were fed by hand twice a day with an interval of 8 h (until apparent satiety). Also, compared to the voluntary feed intake by self-feeder approaches

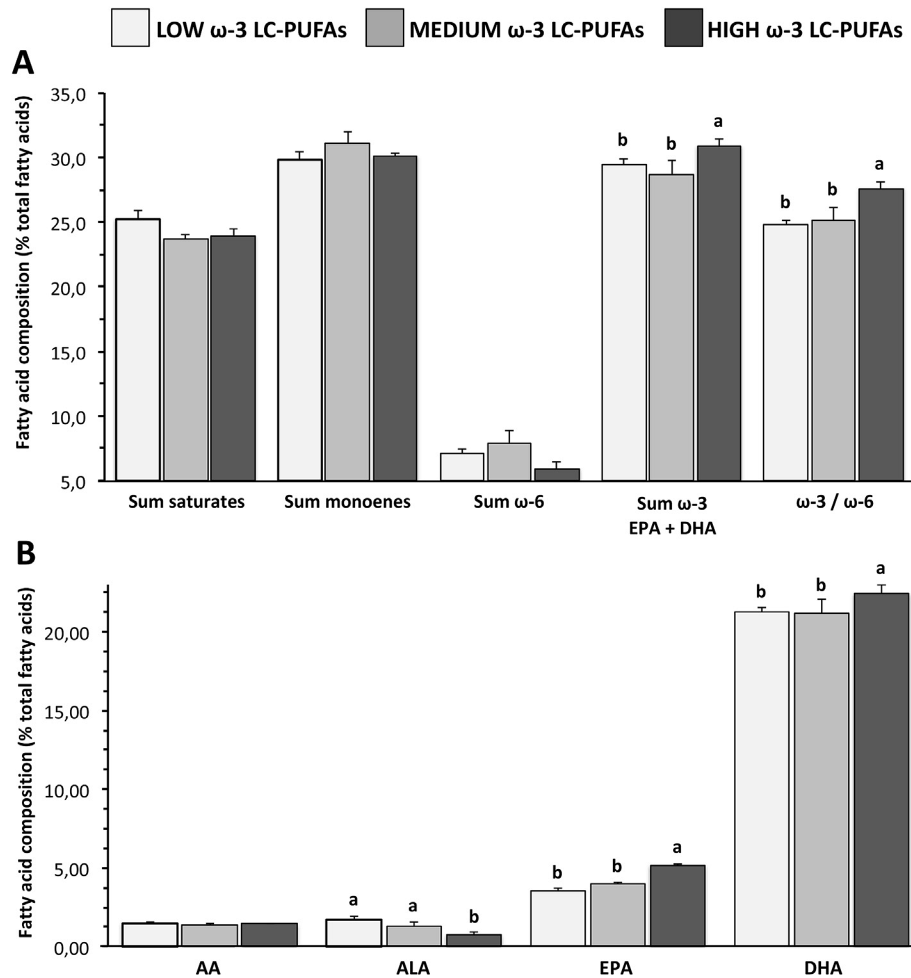

Fig. 1. Representative (A) summary of main fatty acid proportion (% of total fatty acid and (B) selected fatty acids: AA, ALA, DHA and EPA in whole brain at the end of the trial (9 weeks). Data are presented as mean ± SEM. p-values were produced by one-way ANOVA followed by Tukey's HSD comparison test. ($p < 0.05$). Mean values that do not share a common letter are significantly different ($p < 0.05$). $n = 8$ whole fish brain.

[42], the fishes in this present work had limited feed to eat due to shorter feeding period (less than 5 min compared to two feeding periods per day during 2.5 h in previous study). Further, it is possible that higher ω-3 LC-PUFAs diet improved satiation in short feeding period accompanied by faster hunger pangs.

In farmed fish, other studies indicated ω-3 LC-PUFAs altered feeding behavior by ω-3 LC-PUFAs diet. In Senegalese sole (*Solea senegalensis*) fed with ω-3 LC-PUFAs (EPA) diet, Conde-Siera et al., observed that fish have a lower food intake compared to control group [32]. This anorectic effect of ω-3 LC-PUFAs are consistent with previous study reported that intracerebroventricular injection of DHA and EPA decreased feed intake compared to saturated fatty acids in rodents [51,52]. The anorectic effect of ω-3 LC-PUFAs could be attributed in brain and lingual tissus by targeting fatty acids receptor. In rodents, these receptors are known to be activated by ω-3 LC-PUFAs and exerted anxiolytic, anti-inflammatory and anti-depressive properties, which could explain anorectic effect [53].

Concerning fatty acid brain modulation by diet, fatty acid brain composition was differently affected by dietary ω-3 LC-PUFAs., The sum of saturated, monounsaturated and ω-6 LC-PUFAs did not differ between the three groups. The sum of ω-3 LC-PUFAs and the ω-3/ω-6 ratio in brain increased with an increase of EPA and DHA in high ω-3 LC-PUFAs diet. These results are consistent with studies showing that dietary ω-3 PUFAs modulated the brain fatty acid composition in various mice models [54].

As explained in the introduction, numerous mammal's models of ω-3 LC-PUFAs modulation are available in the literature. Fatty acids precursors and their mediators in central nervous system function and disease were previously reported in mammals [3]. A study demonstrated that total fatty acid brain composition of mammals is structure-dependent, strain-specific and differently affected by dietary approaches [54]. Moreover, the present study revealed that DHA content of trout brain tissue (Table 4) was higher than the EPA content (20–22% v. 3–5%) as observed in mammals [54]. In mammals, upon entry into the brain, most LC-PUFAs especially DHA and AA are activated and achieved to phospholipid membranes. Other LC-PUFAs, such as ALA and EPA, are β-oxidized [55]. In addition, knowing that fatty acid in the membrane phospholipid are important for the function of neurotransmitter receptor, DHA has been suggested to be the most important ω-3 LC-PUFAs for brain function [3]. Our findings that DHA is the major ω-3 LC-PUFAs in the brain and that marginal EPA level was observed in brain level of juveniles rainbow trout support these conclusions. Moreover, modulation of brain lipid composition in ω-3 LC-PUFAs (DHA, EPA and ALA) was significantly influenced by dietary ω-3 LC-PUFAs composition. However, even DHA is the most important ω-3 LC-PUFAs in trout brain, marginal effect of ω-3 LC-PUFAs diet supplementation was observed (21.28% for low 21.15% for medium and 22.42% for high ω-3 LC-PUFAs diet). Firstly, it is important to note that all trout

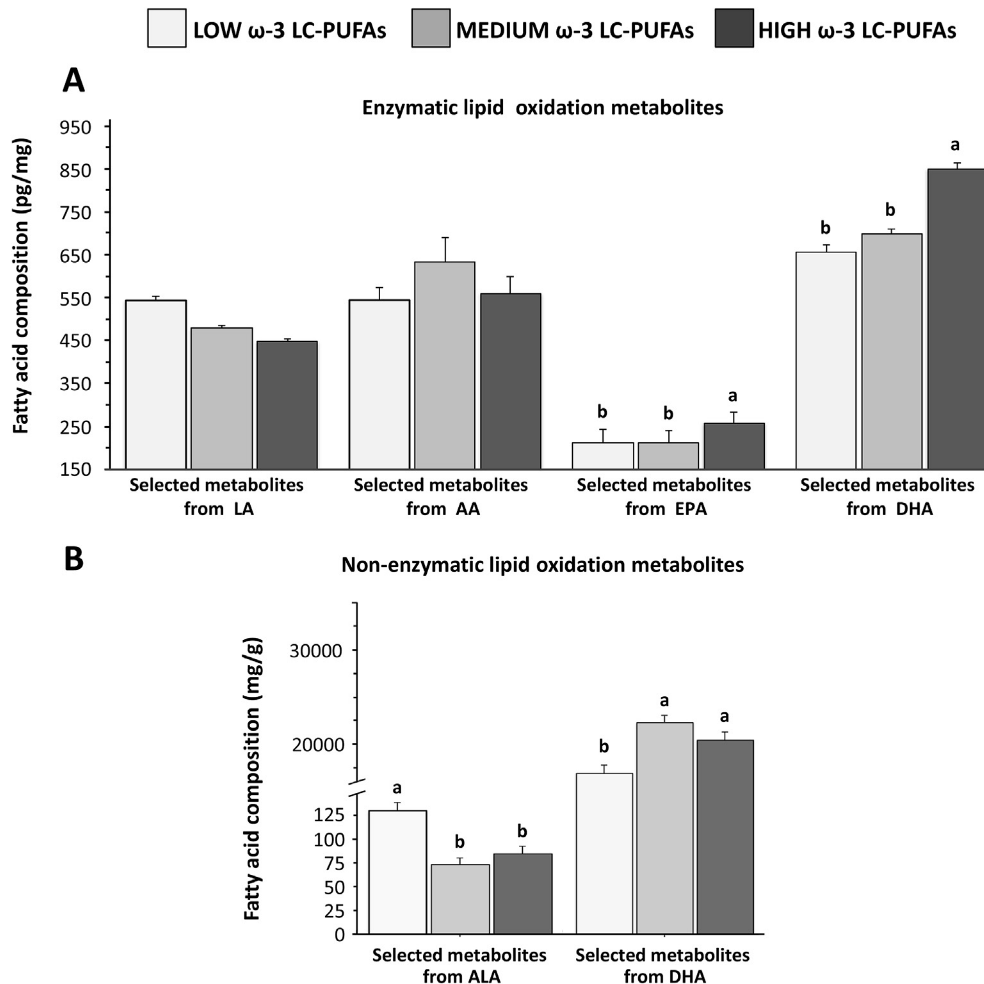

Fig. 2. Representative (A) selected enzymatic (pg/mg) and (B) non-enzymatic (mg/g) lipid oxidation metabolites of whole brain tissues. Data are presented as mean ± SEM. p-values were produced by one-way ANOVA followed by Tukey's HSD comparison test. ($p < 0.05$). Mean values that do not share a common letter are significantly different ($p < 0.05$). $n = 8$ whole fish brain. COX: cyclooxygenases enzymes; LOX: lipoxygenases enzymes; CYP450: cytochromes P450 enzymes; AA: arachidonic acid; EPA: eicosapentaenoic acid; DHA: docoxahexaenoic acid.

prior to the start the experiment were fed with commercial diet containing 10% of DHA (total fatty acid). Secondly, brain lipid content in low ω-3 LC-PUFAs revealed important level of DHA even without supplementation. Thirdly, the majority of fatty acids in brain tissues are in phospholipidic forms and in general, the majority of fatty acid composition of phospholipids are little affected. Finally, some studies observed that structure of lipids in diet influenced the accretion of PUFAs in some tissues. Indeed, phospholipid PUFAs more effectively targets the brain than triglyceride PUFAs [56]. In our study, DHA and EPA were brought by omegavie marine oils, mainly in triglycerides form. These different points could support the marginal effects of ω-3 LC-PUFAs on the DHA level in brain.

Advances on mechanisms in resolution of acute inflammation uncovered a new genus of pro-resolving lipid mediators that include separate families of molecules: lipoxins, resolvins, protectins and maresins [57]. Mouse and human brain have the capacity to produce these enzymatic metabolites of ω-3 LC-PUFAs, resolvins and protectins, which may reduce cytokine expression in human brain cells [58,59]. To date, due to the low proportion of EPA in brain tissue, the few known enzymatic metabolites come mainly from DHA, including neuroprotectin D1, maresin 1, resolvin D5, 17S-hydroxy-DHA and 14-HDHA, all identified within brain regions [57,60,61]. In trout, Hong et al. (2003), revealed for the first time *in vitro* the capacity of trout brain cells to biosynthesize enzymatic metabolites of DHA. They identified resolvin D1, D2, D5 and neuroprotectin D1 from trout brain cells [59]. The enzymatic metabolites of DHA conversion by lipoxygenases, were also identified. These included both 14*S*- and 17*S*-hydroxy-docosahexaenoic acid. In fish cell, the biosynthesis of resolvins and protectins, these novel bioactive lipid mediators provides the first evidence for the conservation of these structures from fish to humans as chemical signals in diverse biological systems. In this study, we also revealed the presence of selected enzymatic metabolites of DHA in rainbow trout brain tissue including the 14*S*-hydroxy-docosahexaenoic acid, the 17*S*-hydroxy-docosahexaenoic acid. These enzymatic metabolites from DHA (lipoxygenases pathways) tend to increased (even not statistically significant) in fish fed the high ω-3 LC-PUFAs diet (Table 5). Even EPA is poorly incorporated in brain tissue, this fatty acid is the precursor of oxylipins which exert numerous functions as neuromodulators [62], inhibits COX-2 [63], and has an effect at genic level [64]. Furthermore, EPA is an inhibitor of phospholipase A2 and may thereby decrease the release of fatty acids (such as DHA) from the phospholipids in the cell membrane including brain tissue [65]. In this study, we characterized the presence of enzymatic oxidation metabolites of EPA in rainbow trout brain tissue

including the 18-hydroxy-eicosapentaenoic acid (18-HEPE) and the prostaglandin E_3. These enzymatic oxidation metabolites from EPA (lipoxygenases) are modulated by the high ω-3 LC-PUFAs diet even did not differ statistically with the diet (Table 5). This metabolite (18-HEPE) was previously observed in human (*in vitro* cell culture), produced hypoxic endothelial cells and acetylated cycloxygenase-2 or cytochrome P450 pathways [66]. 18-HEPE was also produced by microbial P450 [67]. We also revealed the presence in trout brain tissue of 9 and 13-hydroxy-octadecadienoic acids, enzymatic metabolites of LA which did not differ with the diet. About enzymatic metabolites of AA, we observed enzymatic metabolites of AA including prostaglandins ($PGF_{2\alpha}$, PGE_2, PGD_2) from cyclooxygenase enzyme, lipoxin A4, and 5-, 8-, 12-, and 15-hydroxyeicosatetraenoic acids (HETE) and 5-Oxo-eicosatetraenoic acids from lipoxygenases enzyme and 5,6–8,9 and 14,15-epoxyeicosatrienoic acid (5,6-EET, 8,9-EET and 14,15-EET) from cytochrome P450 pathways. Enzymatic metabolites from lipoxygenases and cytochrome P450 tend to decreased and significantly decreased from cycloxygenase in brain tissue of rainbow trout fed with high ω-3 LC-PUFAs diet (Table 5).

Since 1990, under autooxidative conditions, diverse types of non-enzymatic metabolites originating from LC-PUFAs, were discovered [68]. Known as prostaglandin isomers (or isoprostanoids) originating from AA, phytoprostanes from ALA, isoprostanes from EPA, neuroprostanes from DHA, and proved to be prevalent in biology. Since the first discovery of isoprostanes as biomarkers of oxidative stress [69], a new field of research was opened. Today, it is accepted that this non-enzymatic oxidation metabolites are not only biomarkers of oxidative stress but are implicated in several physiological processes [68]. They serve as homeostatic mediators in keeping physiological functions, have inflammatory and immunity properties that are associated to the pathology of diseases [16].

In 2005, non-enzymatic metabolites were identified in rodent brain [70]. Previously, researchers found that 4(*RS*)-4-F_{4t}-NeuroP are increased in humans brain with Alzheimer disease supporting an increase of non-enzymatic oxidation of DHA in this disease [71,72]. In support of these previous studies, our results confirmed that selected non-enzymatic oxidation metabolites of fatty acid such as phytoprostanes from ALA and neuroprostanes from DHA (Table 6) were present in trout brain and modulated by the diet. Total selected non-enzymatic oxidation metabolites from DHA increased with the high ω-3 LC-PUFAs diet whereas those from ALA decreased (Fig. 2B). Knowing that EPA are more β-oxidized and poorly accumulated than DHA into the brain [55], we confirmed higher proportion of total selected non-enzymatic oxidation metabolites of DHA than of EPA. Indeed, we had not detected non-enzymatic oxidation metabolites of EPA.

Several physiological processes were also previously attributed to these metabolites from ω-3 LC-PUFAs. In 2014, Minghetti and coworkers revealed neuroprotective effects of B1-PhytoPs by promoting oligodendrocyte differentiation partly via PPARγ activation for undifferentiated (not for differentiated), SH-SY5Y cells from H_2O_2 insult [73]. About non-enzymatic oxidation metabolite of EPA, Jamil et al. investigated the ability of the 5-F_{3t}-IsoP to regulate glutamatergic neurotransmission [74]. These authors also revealed the neuroprotective role of 5-F_{3t}-IsoP to decrease the progression of ocular neuropathic disease (by reducing excitatory neurotransmitter release). A proarrhythmic property of 5-F_{3t}-IsoP was also revealed on mouse cardiac cells [75]. For non-enzymatic oxidation metabolite of DHA, numerous studies observed biological activities and physiological functions of 4(*RS*)-4-F_{4t}-NeuroP or 10(*R*)-F_{4t}-NeuroP [22,23,76].

5. Conclusion

In conclusion, for the first time, this study revealed the presence of some selected enzymatic and non-enzymatic oxidation metabolites in brain rainbow trout and the modulation of brain lipid content by dietary ω-3 LC-PUFAs, DHA and EPA, in a farm fish species. Knowing the biological activities of some metabolites, further studies have to be performed to characterize and demonstrate the impact on brain function and physiological effect of the presence of this selected enzymatic and non-enzymatic oxidation metabolites in fish models.

Finally, in parallel of this study, a recently study published of this experiment [39] revealed a central regulation by dietary ω-3 LC-PUFAs with regulation of brain mechanisms including oxidant and inflammatory status, stress pathways and genes modulating animal behavior These knowledges obtained and the present study revealed concomitantly the essential implication of dietary ω-3 LC-PUFAs (and potentially their oxidative by-product) in brain lipid configuration and function of juvenile trout trough mechanisms comparable to those characterized previously in mammals.

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Author's contributions

J.R., C·O., JM.G., G.C., and T.D designed and managed the study. J.R. wrote the manuscript, J.V., B.Z., C·O., JM.G., G.C., and T.D contributed to the manuscript corrections. L.L., analysed lipids contents, A.S. analysed diets composition. C.V and G.R analysed selected enzymatic oxidation metabolites A.L., F·S., and F.T. conducted the study at the experimental facilities.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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