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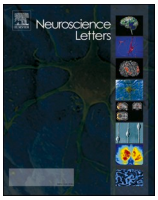

Probing changes in brain esterified oxylipin concentrations during the early stages of pathogenesis in Alzheimer's Disease transgenic rats

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ABSTRACT

Despite known pathological hallmarks of Alzheimer's Disease (AD) including neuronal loss, gliosis (inflammation), beta-amyloid plaque deposition and neurofibrillary tangle accumulation in the brain, little is known about inflammation resolution in early AD pathogenesis. In the brain, inflammation and resolution pathways are mediated by free oxylipins which are mostly bound (i.e. esterified), and therefore must be released (i.e. become free) to exert bioactivity. Recently, we showed reductions in brain esterified pro-resolving oxylipins in a transgenic rat model of AD (TgF344-AD rat) at 15 months of age, suggesting deficits in the source and availability of free pro-resolving oxylipins. In the present study, we tested whether these changes are discernable earlier in the disease process, i.e., at age of 10 months. We observed significant reductions in esterified pro-resolving 8(9)-epoxyeicosatrienoic acid (8(9)-EpETrE), 13-hydroxyoctadecatrienoic acid (13-HOTrE) and 15-hydroxyeicosapentaenoic acid (15-HEPE) oxylipins, and in pro-inflammatory 13-hydroxy-octadecadienoic acid (13-HODE), 20-hydroxy-eicosatetraenoic acid (20-HETE), 15-deoxy-prostaglandin J2 (15-deoxy-PGJ2) and prostaglandin E2 (PGE2) oxylipins in male and/or female transgenic AD rats compared to wildtype controls. These findings point to a deficit in esterified pro-resolving lipid mediators in the early stages of AD, concident with. changes in esterified lipid mediators involved in promoting inflammation.

1. Introduction

Alzheimer's Disease (AD) is an incurable progressive brain disorder that affects more than 11 % of individuals above the age of 65 [1]. AD is characterized by age-dependent changes in mood and cognition, amyloid and tau accumulation in the brain, and microglial activation and astrocytosis characteristic of neuroinflammation (reviewed in [14]).

In a pathologically normal brain, inflammation is kept at bay through an active resolution process enabled by 'pro-resolving' lipid mediators (i.e. oxylipins) enzymatically derived from polyunsaturated fatty acids. Enzymes involved in lipid mediator synthesis are lipoxygenase (LOX), cyclooxygenase (COX), cytochrome P450 (CYP), soluble epoxide hydrolase (sEH) and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) (Reviewed in [9]). Oxylipins can have both pro-inflammatory and pro-resolving effects in vivo [9]. For instance, some arachidonic acid (AA)-derived hydroxyeicosatetraenoic acids (HETEs) and prostanoids (e.g. prostaglandin E2) are known to promote inflammation, whereas epoxides of AA, eicosapentaenoic acid (EPA) and docosahexaenoic (DHA) promote the resolution of inflammation.

It is thought that unresolved inflammation in the brain contributes to AD worsening over time [6,11,19,29,31,32,34,35]. This is evidenced by studies in human cerebrospinal fluid and post-mortem brain, as well as transgenic mouse models showing that in AD, pro-inflammatory lipid mediators such as HETEs and dihydroxyeicosatrienoic acids (DiHETrEs) are elevated [8,20,26,29,31,33,35], whereas pro-resolving oxylipins (neuroprotectin D1, maresin 1, lipoxin A4 (LXA4), epoxydocosapentaenoic acids (EpDPEs), and epoxyeicosatrienoic acids (EpETrEs)) are reduced compared to unaffected controls [6,11,19,29,31,32,34,35]. Collectively, the evidence points to impaired lipid-mediated resolution pathways in AD, concomitant with persistent

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inflammation.

To date, studies have measured free (unesterified) pro-resolving oxylipins in the brain of transgenic mice modelling some aspects of AD pathology in humans, and in postmortem brain of AD patients [6,11,19,29,31,32,34,35]. Yet, in the brain, the majority of oxylipins (~90 %) are bound (i.e. esterified) to neutral lipids (NLs) such as triacylglycerols and cholesteryl esters, and to membrane phospholipids (PLs) [23,30]. The esterified oxylipin pool serves as an important modulator of free oxylipin concentrations via a turnover pathway which releases and re-esterifies free oxylipins [23]. This turnover pathway regulates the in vivo bioavailability of free oxylipins, which is the bioactive pool that mediates inflammation and inflammation resolution [22,27]. In contrast, esterified oxylipins are less biologically active, despite serving as a source or reservoir for free oxylipins [16,21].

Our group has found that pro-resolving lipid mediators are selectively and markedly reduced within brain esterified lipid pools of transgenic AD female rats expressing mutations in the human Swedish amyloid precursor protein (APPswe) and exon 9 presenilin-1 (PS1ΔE9) [28]. Because esterified oxylipins regulate free oxylipin bioavailability, our findings point to sex-specific deficits in the source of free pro-resolving oxylipins in AD. This is in agreement with studies showing reduced concentrations of free pro-resolving oxylipins in the brain of AD patients and transgenic animal models of AD [6,11,19,29,31,32,34,35].

In our prior work involving AD transgenic rats, we measured esterified pro-resolving oxylipins in 15-month old animals [28], when AD pathology and behavioral impairments were established [25]. In the present study, we tested whether changes in esterified oxylipins are discernable earlier in the disease process. Mass-spectrometry was used to quantify NL- and PL-bound oxylipins in one brain hemisphere of 10-month-old animals because at that age, AD transgenic rats show no signs of cognitive impairment or phosphorylated tau accumulation in the brain [25], but present with evidence of beta-amyloid deposition and microglial activation, although less compared to 15 month old animals [25]. Both male and female rats were tested to determine whether sex differences in oxylipin metabolism exist, in view of our prior observations showing changes in esterified oxylipins in AD transgenic rat females but not males, and the higher epidemiological prevalence of AD in females compared to males [3,7].

2. Material and methods

2.1. Animals

Animal protocols were approved by the University of California, Davis (UC Davis) Institutional Animal Care and Use Committee (IACUC). The overall experimental design is shown in Supplementary Fig. 1. Male and female transgenic AD rats (TgF344-AD) and wildtype littermates (WTF344) were bred at UC Davis [25] and the resulting offspring consisting of 26 male and female TgF344-AD and WTF344 rats were transferred on postnatal day 28, to a tunnel facility in Northern California [10], where they received filtered air. This subset of animals was part of a broader study examining the effects of traffic-related air pollution on AD phenotypes in rats [10,25]. We focused the present analysis on AD and wildtype (WT) rats exposed to filtered air only. Rats were transported back to UC Davis after 9 months. They were euthanized 2 days later with 4 % isoflurane (Southmedic Inc., Barrie ON) and brain samples were harvested [25].

2.2. Brain NL and PL oxylipin analysis

Esterified oxylipins were extracted from the right hemisphere with 6 mL of 2:1 chloroform/methanol and 700 μL aqueous buffer containing 1 mM Na_2EDTA and 0.9 % NaCl, followed by a repeated 4 mL of chloroform extraction, as previously described [28]. The total lipid extract was reconstituted in 2:1 v/v chloroform/isopropanol and a 300 μL volume containing ~ 3 mg total lipids was subjected to solid phase extraction (SPE) on Waters silica columns (Sep-Pak Silica, 1 cc, 100 mg, Waters Corporation, Milford, MA; Cat #WAT023595) preconditioned with methanol (1.5 mL) and 2:1 v/v chloroform/isopropanol (1.5 mL). NLs were eluted with 1.5 mL of chloroform/isopropanol (2:1 v/v). The silica column was washed 1.5 mL of 95 % methanol, and the eluent containing PLs was adjusted to 80 % methanol and then loaded onto Waters tC18 columns (Sep-Pak tC18, 1 cc, 100 mg, Cat #WAT036820) preconditioned with one column volume of methanol and 1.5 mL of 80 % methanol. The column was washed with 2 mL of 80 % methanol, followed by 2 mL pure methanol to elute PLs.

NL and PL fractions were reconstituted in 200 μL of methanol containing 0.1 % acetic acid and 0.1 % butylated hydroxytoluene (BHT), 10 μL of antioxidant solution (0.2 mg/mL BHT, ethylenediaminetetraacetic acid and triphenylphosphine in 1:1 water/methanol), 10 μL of 2 μM surrogate standard mix (of d11-11(12)-EpETrE, d11-14,15-DiHETrE, d4-6-keto-PGF1a, d4-9-HODE, d4-LTB4, d4- PGE2, d4- thromboxane B2 (TXB2), d6-20-HETE, and d8-5-HETE in LC-MS grade methanol), and 200 μL of 0.25 M NaOH in 1:1 water/methanol. The mixture was vortexed, hydrolyzed at 60 °C for 30 min on a heating block and cooled at room temperature for ~ 5 min. The reaction was stopped with 25 μL of acetic acid and 1575 μL of MilliQ water. Samples were loaded onto Waters Oasis HLB columns (3 cc, 60 mg, 30 μm particle size; Waters Corporation, Cat #WAT094226) pre-rinsed with one column volume of ethyl acetate and two volumes of methanol, and pre-conditioned with two column volumes of SPE buffer containing 0.1 % acetic acid and 5 % methanol in MilliQ water. Upon loading the samples, the columns were washed with two column volumes of SPE buffer, dried under vacuum (≈15–20 psi) for 20 min. Oxylipins were eluted with 0.5 mL methanol and 1.5 mL ethyl acetate into 2 mL centrifuge tubes, reconstituted in 100 μL LCMS grade methanol, and filtered using 0.1 μm Centrifugal Filters (Millipore Sigma, Burlington, MA, USA; Cat # UFC30VV00).

A total of 76 oxylipins per lipid pool were analyzed by ultra high-pressure liquid chromatography-tandem mass spectrometry as previously described [28].

2.3. Statistical analysis

GraphPad Prism v.8.02 (La Jolla, CA, USA) software was used for data analysis. Missing oxylipin values (up to 3 per group) were imputed by dividing the lowest observable concentration on the standard curve by the square root of 2. The number of imputed oxylipin values per group is shown in Supplementary Table 1.

The effects of sex and genotype on brain NL and PL oxylipins were examined by two-way analysis of variance (ANOVA). The effects of genotype on brain NL and PL oxylipins per sex were determined by an unpaired Student's *t*-test followed by Benjamini and Hochberg correction at a false discovery rate (FDR) of 1 %, given the small sample size (6–8 per group per sex) and preliminary nature of the study [4]. Statistically significant values were accepted at $p < 0.05$ and at $q < 0.01$.

3. Results

3.1. Effects of AD genotype on NL-bound oxylipins in brain of 10-month-old rats

Two-way ANOVA showed that sex was a significant factor affecting linoleic acid (LA)-derived 9-octadecadienoic acid (9-oxo-ODE), AA-derived 15-HETE, LXA4 and prostaglandin F2a (PGF2a), EPA-derived 15-hydroxyeicosapentaenoic acid (15-HEPE), and DHA-derived 17-hydroxydocosahexaenoic acid (17-HDoHE), 19(20)-EpDPE, 16(17)-EpDPE and 7(8)-EpDPE in brain NLs, which were 18 %-102 % higher in females than males ($p < 0.05$; Supplementary Table 2).

Genotype significantly altered EPA-derived 15-HEPE, and DHA-derived 16,17-dihydroxydocosapentaenoic acid (16,17-DiHDPA) ($p < 0.05$; Supplementary Table 2). 15-HEPE was lower by 14 % in AD transgenic rats compared to WT controls (Fig. 1-a), whereas 16,17-

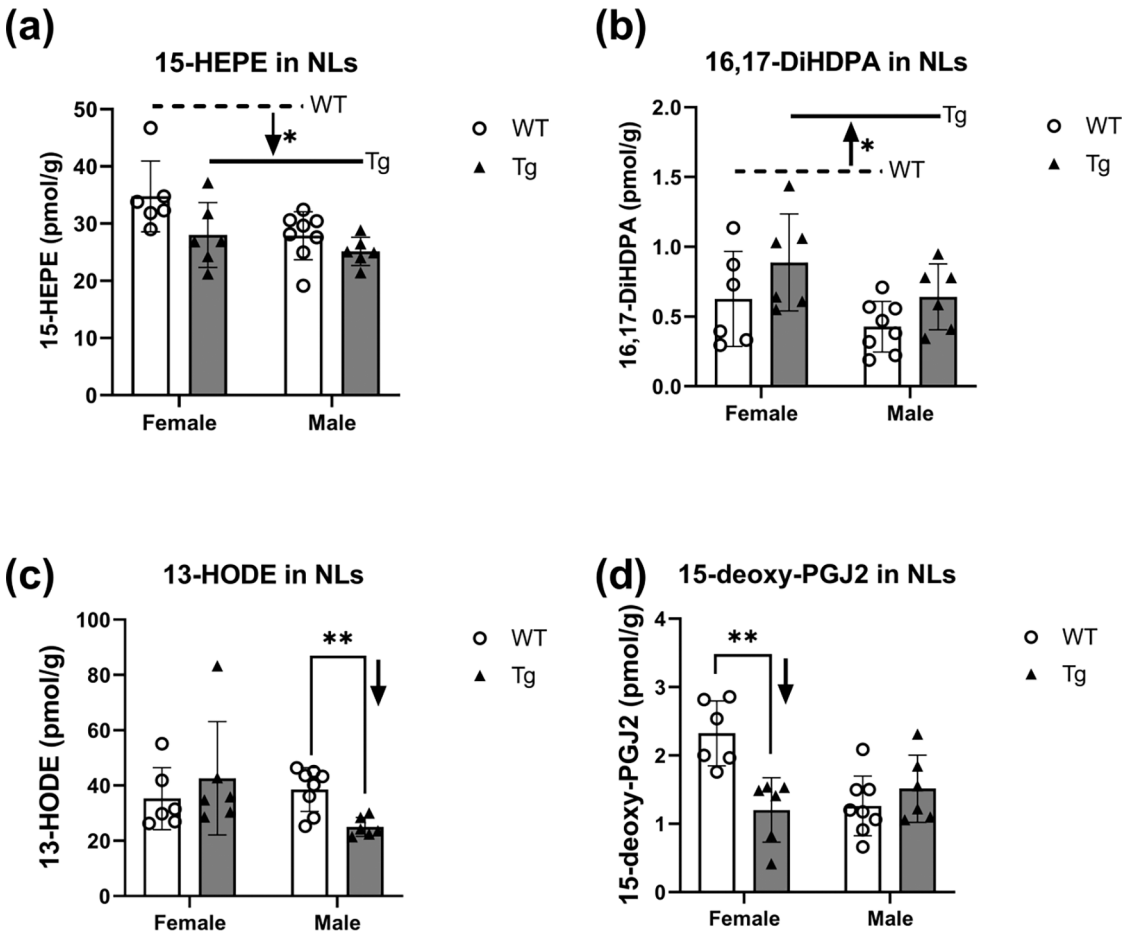

Fig. 1. Oxylipin concentrations (pmol/g) in brain neutral lipids (NLs) of 10-month-old wildtype (WT) and TgF344-AD (Tg) female and male rats: (a) 15 hydroxy-eicosapentaenoic acid (15-HEPE); (b) 16,17-dihydroxy-docosapentaenoic acid (16,17-DiHDPA); (c) 13-hydroxy-octadecadienoic acid (13-HODE); (d) 15-deoxy-prostaglandin J2 (15-deoxy- PGJ2). The sample size per group was: Female WT, n = 6); female Tg, n = 6); male WT, n = 8; male Tg,n = 6. Two-way ANOVA revealed significant effects of genotype on 15-HEPE and 16,17-DiHDPA, and a significant interaction between genotype and sex on 13-HODE and 15-deoxy-PGJ2. An asterisk (*) between the dashed line and solid line on top of some of the graphs denotes significance at $p < 0.05$ by two-way ANOVA irrespective of sex. Two Asterisks (**) between bars comparing two groups denote significance at $p < 0.05$ and $q < 0.01$ by unpaired *t*-test with false discovery rate (FDR) correction per sex.

DiHDPA was 49 % higher in AD versus WT rats, irrespective of sex (Fig. 1-b).

Significant sex and genotype interaction effects were observed in LA-derived 13-hydroxyoctadecadienoic acid (13-HODE), and AA-derived 20-HETE, 15-oxo-eicosatetraenoic acid (15-oxo-ETE) and 15-deoxy-prostaglandin J2 (15-deoxy-PGJ2) ($p < 0.05$; Supplementary Table 2). A main genotype effect was also observed for 15-deoxy-PGJ2 ($p < 0.05$; Supplementary Table 2).

Post-hoc comparison of AD versus WT rats, per sex, by unpaired Student's *t*-test with FDR correction revealed a 35 % reduction in LA-derived 13-HODE in TgF344-AD males compared to WT males (Fig. 1-c, $p = 0.0022$, $q = 0.0044$) and a 48 % reduction in AA-derived 15-deoxy-PGJ2 in TgF344-AD females compared to WT females (Fig. 1-d, $p = 0.0021$, $q = 0.0043$). No significant differences per sex were observed for 20-HETE and 15-oxo-ETE by post-hoc comparison using an unpaired *t*-test with FDR correction (Supplementary Table 2).

3.2. *Effects of AD genotype on PL-bound oxylipins in brain of 10-month-old rats*

Two-way ANOVA showed that sex was a significant factor affecting LA-derived 12(13)-epoxyoctadecenoic acid (12(13)-EpOME) and 9(10)-EpOME, dihomo-gamma-linoleic acid (DGLA)-derived 15(S)-hydroxyeicosatrienoic acid (15(S)-HETrE), AA-derived 14(15)-EpETrE, 11(12)-EpETrE, 8(9)-EpETrE, 5(6)-EpETrE, 11,12-dihydroxyeicosatrienoic acid (11,12-DiHETrE), 8,9-DiHETrE and LXA4, alpha-linolenic acid (ALA)-derived 13-hydroxyoctadecatrienoic acid (13-HOTrE), EPA-derived 14 (15)- epoxyeicosatetraenoic acid (14(15)-EpETE) and Resolvin E1, and DHA-derived 19(20)-EpDPE, 16(17)-EpDPE, 13(14)-EpDPE, 7(8)-EpDPE and 19,20-DiHDPA in brain PLs ($p < 0.05$; Supplementary Table 3). These compounds were 24 %-800 % higher in females than males.

Genotype significantly altered AA-derived 20-HETE (Fig. 2-a), 8(9)-EpETrE (Fig. 2-b) and prostaglandin E2 (PGE2; Fig. 2-c), and ALA-derived 13-HOTrE (Fig. 2-d), which were all lower by 11–49 % in AD compared to WT rats, irrespective of sex ($p < 0.05$; Supplementary Table 3).

A significant sex and genotype interaction was observed in EPA-derived 11(12)-EpETE, and DHA-derived 16,17-DiHDPA ($p < 0.05$; Supplementary Table 3). Post-hoc unpaired *t*-test analysis with FDR correction applied per sex revealed significant genotype differences in 16,17-DiHDPA but not 11(12)-EpETE concentrations. DHA-derived 16,17-DiHDPA was 37 % lower in TgF344-AD males compared to WT males (Fig. 2-e, $p = 0.0037$, $q = 0.0074$); no significant differences were observed in females.

4. Discussion

This study provides evidence of sex-specific brain changes in esterified lipid mediators involved in inflammation and inflammation

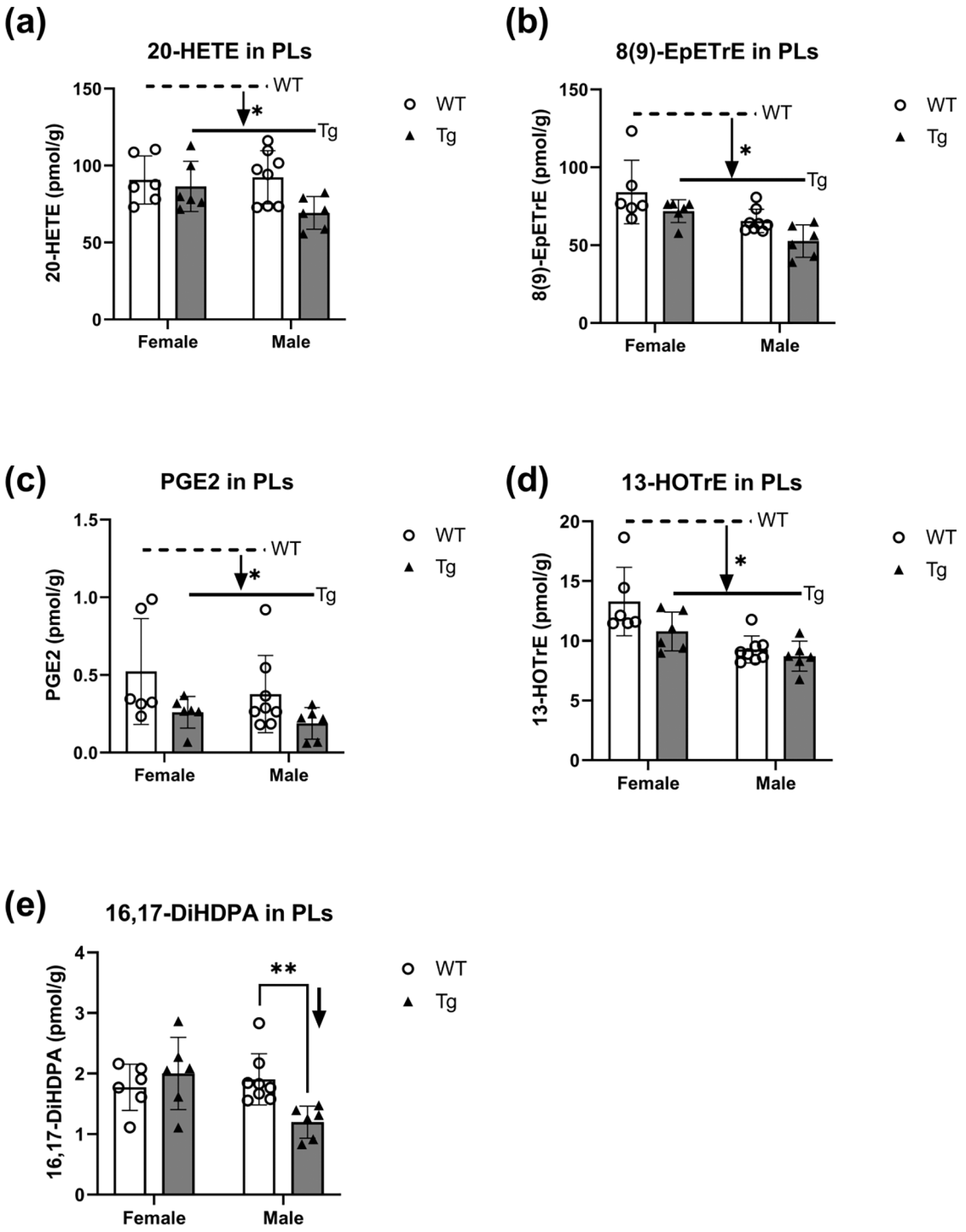

Fig. 2. Oxylipin concentrations (pmol/g) in brain phospholipid (PLs) of 10-month-old wildtype (WT) or TgF344-AD (Tg) female and male rats: (a) 20-hydroxy-eicosatetraenoic acid (20-HETE); (b) 8(9)-epoxy-eicosatrienoic acid (8(9)-EpETrE); (c) prostaglandin E2 (PGE2); (d) 13-hydroxy-octadecatrienoic acid (13-HOTrE); (e) 16,17-dihydroxy-docosapentaenoic acid (16,17-DiHDPA). Two-way ANOVA revealed significant effects of genotype on 20-HETE, 8(9)-EpETrE, PGE2, and 13-HOTrE, and a significant sex and genotype interaction on 16,17-DiHDPA. The sample size per group was: Female WT, n = 6;, female Tg, n = 6; male WT, n = 8; male Tg, n = 6. An asterisk (*) between the dashed line and solid line on top of some of the graphs denotes significance at $p < 0.05$ by two-way ANOVA irrespective of sex. Two Asterisks (**) between bars comparing two groups denote significance at $p < 0.05$ and $q < 0.01$ by unpaired *t*-test with false discovery rate (FDR) correction per sex.

resolution in 10-month old AD transgenic rats, coincident with the onset of microglial activation and β-amyloid plaque accumulation [25]. We observed significant reductions in both pro-resolving (AA-derived 8(9)-EpETrE, ALA-derived 13-HOTrE and EPA-derived 15-HEPE) and pro-inflammatory (AA-derived 20-HETE, 15-deoxy-PGJ2 and PGE2, and LA-derived 13-HODE) esterified oxylipins in male and/or female transgenic AD rats compared to WT controls. DHA-derived 16,17-DiHDPA, a diol fatty acid metabolite of pro-resolving 16(17)-EpDPE, was elevated in NLs of AD rats independent of sex, and reduced in PLs of 10-month old male AD rats.

The reduction in esterified pro-resolving lipid mediators at 10 months reflects early impairments in resolution pathways. Esterified oxylipins are a source of free and bioactive pro-resolving oxylipins [23] which halt inflammation [13,22] and promote neuronal survival [5,34]

and axonal outgrowth [2] via specialized G-protein coupled receptors [16,18]. Thus, reductions in esterified pro-resolving oxylipins are likely due to increased utilization (i.e. release via lipase enzymes) and turnover into free bioactive oxylipins that might contribute to inflammation resolution during the early phases of the disease. In the later phases of the disease, as more esterified pro-resolving lipid reserves become depleted [28], the availability of free pro-resolving oxylipins may decrease, consistent with studies showing reduced levels of free AA-derived epoxides (EpETrEs) in transgenic mouse models of AD after disease pathology is established [6,11,29].

A few pro-inflammatory oxylipins derived from omega-6 LA (13-HODE) and AA (20-HETE, 15-deoxy-PGJ2 and PGE2) decreased in brain esterified lipid pools of AD rats compared to WT controls at 10 months. These changes may be due to increased release or reduced esterification of free pro-inflammatory lipid mediators, coincident with inflammation seen in the brain of these animals at 10 months of age [25]. Studies have shown elevated free PGE2 concentrations in cerebrospinal fluid of AD patients [8,20], although temporal changes in free PGE2 and other lipid mediators in this transgenic rodent model of AD remain to be confirmed.

DHA-derived 16,17-DiHDPA, an sEH product of 16(17)-EpDPE, was elevated in NLs of both sexes and reduced in PLs of 10-month-old male AD rats. It is possible that in males, 16,17-DiHDPA in PLs was remodeled into NLs, which could explain the increase seen there. Another explanation for the increase in NL-bound 16,17-DiHDPA is increased esterification, secondary to elevated sEH activation. sEH itself is not known to esterify oxylipins directly, but increased sEH activity reported in transgenic animal models of AD [29] may lead to excess free fatty acid diols which can then be sequestered into esterified lipids via acyl-CoA synthetase and acyltransferase enzymes [15,17].

Of the lipid mediators that changed at 10 months, only PL-bound 8(9)-EpETrE and PGE2 overlapped and paralleled the reductions seen at 15 months in AD rats [28]. Additionally, 15-HEPE decreased in NLs at 10 months and in PLs at 15 months, whereas 20-HETE decreased in PLs at 10 months and in NLs at 15 months [28]. Collectively, these data reflect a progressive decline in esterified pro-resolving (8(9)-EpETrE and 15-HEPE) and pro-inflammatory (PGE2 and 20-HETE) lipid mediators with time, albeit within different esterified lipid pools in some cases possibly due PL/NL remodeling. Of note, many of the changes in esterified oxylipins at 15 months were seen in pro-resolving species [28], unlike pro-inflammatory lipid mediators which were confined to a few compounds between time-points, possibly due to enhanced engagement of resolution pathways with disease progression.

In AD transgenic rats, more esterified oxylipins decreased at 15 months compared to 10 months of age (reductions in 8 oxylipins at 10 months versus 22 oxylipins at 15 months) [28]. These changes may be associated with temporal changes in disease progression. For instance, 15-month old TgF344-AD rats had more amyloid plaque deposition, higher hyperphosphorylated tau levels, more neuronal cell loss, and greater cognitive deficits than 10-month old rats [25]. It is difficult to establish which pathogenic factors altered esterified lipid mediators at 10 months. However, it appears that both the lipid mediators and pathology worsened over time. Future studies should explore whether blocking changes in esterified lipid mediator levels alter the progression of AD pathologies and cognitive impairment in transgenic AD rats.

Surprisingly, more changes in AD males were observed at 10 versus 15 months [28]. Specifically, NL-bound 13-HODE and PL-bound 16,17-DiHDPA were reduced in AD males at 10 months, but not at 15 months. It is not clear why the changes in males were transient. Males are more resilient to AD pathogenic changes than females. For instance, female transgenic AD rats exhibit Aβ proteinopathy earlier than males, and also show greater microglial activation relative to males [25]. In humans, females have twice the risk of AD compared to males [3,24]. It is possible that adaptive mechanisms in esterified oxylipin turnover in males may explain sex differences in disease resiliency and progression.

The main limitation of this study is that free oxylipins were not measured. We did not elect to do so because unlike esterified oxylipins, free oxylipins are sensitive to the effects of postmortem ischemia. For instance, a 155-fold increase in brain free oxylipin concentrations was reported following post-mortem ischemia [12] compared to a 27–112 % increase in esterified oxylipins [23]. Another limitation is that the hydrolysis procedure for liberating esterified oxylipins results in the destruction of some oxylipins such as prostaglandins [30]. Although this limits quantitation, relative differences would still be valid. In this study, key pathological and behavioral hallmarks of AD were not measured, thus limiting our ability to directly correlate the lipid changes to AD-phenotypes.

In conclusion, we showed early-onset reductions in 4 pro-resolving lipid mediators or their diol metabolite, and 4 pro-inflammatory oxylipins within PLs and/or NLs of 10-months old transgenic AD rats. With age, more pro-resolving lipid mediators were reduced in esterified lipid pools of AD rats [28]. Age-dependent reductions in pro-resolving esterified lipid mediators may contribute to impaired resolution of inflammation in AD.

CRediT authorship contribution statement

Qing Shen: Formal analysis, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Kelley T. Patten:** Investigation, Writing – review & editing. **Anthony Valenzuela:** Investigation. **Pamela J. Lein:** Conceptualization, Funding acquisition, Writing – review & editing. **Ameer Y. Taha:** Conceptualization, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing.

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.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neulet.2022.136921.

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