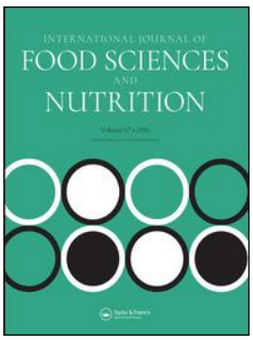

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RESEARCH ARTICLE

Increasing dietary EPA and DHA influence estimated fatty acid desaturase activity in systemic organs which is reflected in the red blood cell in mice

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ABSTRACT

Delta-5 (D5D) and delta-6 (D6D) desaturase are key enzymes in fatty acid (FA) metabolism. Dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may alter tissue FA composition via D5D and D6D. The purpose was to determine the relationship between dietary EPA + DHA, estimated desaturase activities of various tissues and the reflection of desaturase activity in the red blood cell (RBC). Mice were fed diets with increasing percent of energy from EPA + DHA. Phospholipid FA composition of heart, muscle, spleen, lung, adipose tissues and RBC were analysed. D5D and D6D enzyme activity estimates (EAE) were calculated as the ratio of 20:4/20:3 and 20:3/18:2, respectively. D5D EAE decreased in all tissues, except muscle, with increasing dietary EPA + DHA. RBC D5D EAE positively correlated with D5D EAE in all tissues. RBC D6D EAE positively correlated with muscle and inversely correlated with adipose D6D EAE. Our findings suggest differential influence of dietary EPA + DHA upon tissue desaturase activities.

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KEYWORDS
Desaturase; DHA; EPA; fatty acid metabolism; PUFA

Introduction

Altered dietary fatty acid (FA) intake is associated with obesity, chronic low-grade inflammation, type-2 diabetes (T2D) and metabolic syndrome (Fekete et al. 2015). In particular, these metabolic disorders are related to dysregulated polyunsaturated fatty acid (PUFA) metabolism (McGarry 2002). Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are omega-3 (n-3) long-chain PUFA (LCPUFA) associated with improved PUFA metabolism, insulin signalling, and inflammation (Carpentier et al. 2006; Von Schacky & Harris 2007). EPA and DHA can be synthesised from n-3 alpha-linolenic acid (ALA), through a series of elongations and desaurations (Sprecher 1981). Omega-6 (n-6) linoleic acid (LNA) can be converted to n-6 LCPUFA using the same enzymes as n-3 biosynthesis (Sprecher 1981). Therefore, altered dietary PUFA intake can lead to increased production of LCPUFA from one omega family (Pawlosky et al. 2003; Hussein et al. 2005), through substrate competition for LCPUFA-generating enzymes (Lorente-Cebrian et al. 2013; Gurzell et al. 2014).

The conversion of essential fatty acids (EFA) ALA and LNA into their respective LCPUFA products are mediated by elongases and desaturases, which results in the formation of EPA and DHA from ALA, and arachidonic acid (ARA) from LNA. The endogenous synthesis of EPA and DHA from ALA is very low (Burdge et al. 2003). Desaturases such as delta-5 desaturase (D5D) and delta-6 desaturase (D6D) are the rate-limiting enzymes responsible for PUFA desaturation (El Boustani et al. 1989; Horrobin 1993, Kröger 2012). The EFA and their downstream LCPUFA products, EPA, DHA and ARA, are competitive substrates for D5D and D6D (Brenner & Peluffo 1966). In addition, PUFA metabolism is also affected by changes in desaturase activity, especially in the pathobiology of diseases linked to altered metabolism (i.e. T2D and obesity) (Kröger 2012; Warensjo et al. 2006). For instance, recent research suggests that decreased D5D and increased D6D activity increase the risk of developing T2D (reviewed in detail (Kröger 2012)). There is an abundance of research investigating desaturase activities in diseases such as obesity; however, the effects of dietary PUFA intake on desaturase activity in non-obese models is largely unexplored.

FA metabolism occurs in most biological tissues and the rate of FA metabolism (i.e. desaturation) can be tissue specific (Frayn et al. 2005, 2006). Direct measurement of tissue desaturase activity requires an invasive biopsy, and it is difficult to justify obtaining

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biopsies from healthy patients. Therefore, researchers employ enzyme activity estimates (EAE), the ratio of FA product-to-precursor, which indirectly estimates tissue FA desaturase activities (Hodge et al. 2007; Krachler et al. 2008; Kröger 2012). D5D and D6D EAE are calculated as the ratio of ARA to dihomo-gamma-linolenic acid (DGLA), and the ratio of DGLA to LNA, respectively. FA levels are frequently measured in red blood cell (RBC) PL fractions (Raatz et al. 2012; Pickens et al. 2016). In fact, desaturase EAE calculated from blood lipid fractions are associated with desaturase activity in tissues (Chajès et al. 2011) such as adipose (Warensjö et al. 2009).

Most studies investigating the potential health benefits of dietary EPA + DHA focus on PUFA metabolism in diseased states, such as obesity and obesity-associated comorbidities (i.e. insulin resistance, T2D and chronic low-grade inflammation) (Kris-Etherton et al. 2002; Simopoulos 2002). Numerous studies examine associations between dietary EPA + DHA, and RBC FA concentrations and FA incorporation into specific tissues (Block et al. 2008; Gurzell et al. 2014; Walker et al. 2014). There is a dearth of research investigating the relationship between dietary EPA + DHA and tissue and RBC desaturase EAE in non-obese states. Determining whether dietary LCPUFA alter estimated desaturase activity in the absence of metabolic diseases (i.e. obesity), may provide new insights into the relationship between dietary PUFA intake, PUFA metabolism and the effects on estimated desaturase activity. Therefore, the objective of this study was to determine whether increasing dietary EPA + DHA alters D5D and D6D EAE in tissues of non-obese mice, and if these alterations are reflected in the RBC.

Materials and methods

Dietary treatment and experimental design

The experimental design and dietary treatment employed in this study have been previously described (Gurzell et al. 2014). In brief, twenty-four SMAD3-/- mice ($n = 6$/group) were fed *ad libitum* standard AIN-93 G diet containing soybean oil (control) or one of three treatment diets containing increasing amounts of EPA + DHA, as previously described (Kris-Etherton et al. 2003). The experimental diets were calculated from the percent energy (%en) a human consuming 2000 kcal would receive from EPA + DHA following the 2002 American Heart Association recommendations (Kris-Etherton et al. 2003). The experimental diets were formulated to model a 2000 kcal human intake with either no fish or fish oil: (1) no fish oil diet (0.0%en EPA + DHA); (2) two servings of fish a week (0.1%en EPA + DHA); (3) 1-2 g fish oil supplementation a day (0.675%en EPA + DHA); or (4) 4 g prescription fish oil a day (1.8%en EPA + DHA). Mice were fed the diets for 5 weeks prior to euthanasia. Tissues were collected, rinsed in cold ddH_2O, frozen on dry ice, and stored in −80 °C until lipid extraction. All animal procedures were previously approved by the Michigan State University All-University Committee on Animal Care and Use (AUF 02/14-031-00).

PL isolation and analysis of fatty acid methyl esters (FAME)

PL isolation and FA methylation were performed as previously described (Gurzell et al. 2014). In brief, total lipid was extracted using a modified Rose and Oklander extraction (Rose & Oklander 1965), PL were isolated using Isolute-XL® SPE aminopropyl columns (500 mg; Biotage, Charlotte, NC) from a procedure modified by Agren et al. (1992). FAME were generated using acidified methanol described by Burdge et al. (2000). Gas chromatography of fatty acid methyl esters were analysed at OmegaQuant Analytics, LLC (Sioux Falls, SD). Gas chromotography was performed using a GC2010 Gas Chromatograph (Shimadzu, Columbia, MD) equipped with a SP2560, 100-m column (Supelco, Bellefonte, PA) using hydrogen as carrier gas. Referenced against a standard of FA characteristic of erythrocytes, PL FA were identified and calculated as a percentage of total identified FA after response factor correction. Reproducibility of this method has been previously reported by Pickens et al. (2016).

Statistical analysis

D5D and D6D EAE were calculated as the ratio of product/substrate. The following desaturases were calculated and used in our analyses: D5D EAE were calculated as the ratio of ARA/DGLA; D6D EAE were calculated as the ratio of DGLA/LNA. Pearson's correlation coefficients were calculated for D5D EAE and D6D EAE across all dietary treatments to evaluate whether RBC D5D EAE and D6D EAE correlate with those of specified tissues. The mean ± SEM for the D5D EAE and D6D EAE across all tissues and dietary treatments are provided in Tables 1 and 2. A Student's *t*-test was performed to compare desaturase EAE of the two lowest (0.0%en EPA + DHA and 0.1%en EPA + DHA) and two highest (0.675%en EPA + DHA and 1.8%en EPA + DHA) dietary treatment groups. A one-way ANOVA and Tukey's

post hoc were performed to test for differences across D5D EAE and D6D EAE in individual tissues for each %en EPA + DHA dose. A G-test was conducted to determine whether there were outliers from the normal distribution; there were no significant outliers to report. Statistical significance was set at the $p < .05$ level. All statistical analyses were conducted using SAS (Statistical Analysis Software, Cary, NC).

Results

Correlations between tissue and RBC D5D and D6D EAE

In general, RBC D5D and D6D EAE were highly correlated with tissue D5D and D6D EAE. RBC D5D EAE were positively correlated with D5D EAE in adipose ($r = 0.73$, $p < .0001$), muscle ($r = 0.64$, $p < .001$), heart ($r = 0.87$, $p < .0001$), lung ($r = 0.66$, $p < .0005$) and spleen ($r = 0.89$, $p < .0001$). RBC D6D EAE were inversely correlated with D6D EAE in adipose ($r = -0.63$, $p < .001$), while RBC D6D EAE were positively correlated with D6D EAE in muscle ($r = 0.67$, $p < .0005$). RBC D6D EAE were not correlated with heart, spleen or lung D6D EAE (Figures 1–2).

Table 1. Tissue delta-5 desaturase (D5D) enzyme activity estimates (EAE) decrease with increasing percent energy (%en) from dietary eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)[a].

	%en EPA + DHA				
D5D EAE	0.0%	0.1%	0.675%	1.8%	*p*-value
Adipose	36.3 ± 11.0^{a}	23.4 ± 6.1^{b}	14.4 ± 1.3^{bc}	8.0 ± 1.9^{c}	$p < .05$
Muscle	18.1 ± 2.3^{ab}	19.5 ± 1.1^{a}	15.7 ± 2.4^{b}	17.0 ± 1.6^{ab}	$p = .07$
Heart	25.4 ± 2.7^{a}	24.8 ± 2.2^{a}	18.0 ± 1.3^{b}	14.6 ± 2.4^{b}	$p < .05$
Lung	15.3 ± 2.3^{a}	12.4 ± 0.5^{b}	9.3 ± 1.0^{c}	6.9 ± 0.6^{d}	$p < .05$
Spleen	20.4 ± 1.7^{a}	19.2 ± 0.9^{a}	12.7 ± 0.6^{b}	9.9 ± 0.6^{c}	$p < .05$

[a]Data are reported as mean ± SEM as the ratio of arachidonic acid/dihomo-gamma-linolenic acid isolated from membrane phospholipid; $n = 6$ mice/group. Individual one-way ANOVAs with Tukey's *post hoc* tests were used to assess significant differences across the different %en EPA + DHA doses within single tissues (lower case letters). Differences between lower case letters imply significant differences at the $p < .05$ level. The *p*-value column represents the overall *p*-value.

Diet-dependent changes in specified tissue D5D EAE and D6D EAE

There was a clear separation in tissue D5D and D6D EAE between the two lowest (0.0%en EPA + DHA and 0.1%en EPA + DHA) and the two highest (0.675%en EPA + DHA and 1.8%en EPA + DHA) dietary treatment groups exhibited. Therefore, further statistical analysis explored a diet-dependent relationship between tissue D5D and D6D EAE and dietary EPA + DHA, and focussed upon comparison between the two lowest and two highest dietary treatment groups (Figure 3).

In adipose, heart, lung and spleen, D5D EAE significantly decreased in the high dietary treatment group compared to the low dietary treatment group. Muscle D5D EAE did not significantly differ between the high- and low-dietary treatment groups. In general, D6D EAE did not significantly differ across tissues when comparing the high- and low-dietary treatment groups. Adipose D6D EAE was slightly increased in the high-dietary treatment group, while muscle was slightly decreased in the high-dietary treatment group, compared to the low-dietary treatment group.

The mean D5D EAE and D6D EAE and statistical differences between %en EPA + DHA treatments for each tissue are presented in Tables 1 and 2. D5D EAE significantly decreased with increasing %en EPA + DHA in all tissues, except D5D EAE tended to be decreased in muscle. When comparing mean D5D EAE of the lowest (0.0%en) and highest (1.8%en) dietary treatment groups, mean D5D EAE was significantly lower ($p > .05$) in all tissues, except for muscle. In contrast, there was no consistent trend in mean D6D EAE (i.e. all increased or all decreased) across all tissues with increasing %en EPA + DHA. Instead, mean D6D EAE significantly increased in adipose, and mean D6D EAE significantly decreased in muscle when comparing the lowest (0.0%en) and highest (1.8%en) dietary treatment groups. In heart, lung, and spleen, mean D6D EAE neither significantly increased nor decreased between the 0.0% and 1.8%en dietary treatment groups.

Table 2. Increased percent energy (%en) from eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) result in tissue-specific differences in delta-6 desaturase (D6D) enzyme activity estimates (EAE)[a].

	%en EPA + DHA				
D6D EAE	0.0%	0.1%	0.675%	1.8%	*p*-value
Adipose	0.018 ± 0.005^{a}	0.029 ± 0.005^{b}	0.027 ± 0.008^{ab}	0.036 ± 0.006^{b}	$p < .05$
Muscle	0.075 ± 0.008^{a}	0.058 ± 0.013^{b}	0.045 ± 0.004^{b}	0.045 ± 0.006^{b}	$p < .05$
Heart	0.038 ± 0.002^{a}	0.039 ± 0.003^{a}	0.040 ± 0.004^{a}	0.041 ± 0.005^{a}	$p < .05$
Lung	0.095 ± 0.008^{ab}	0.102 ± 0.006^{a}	0.101 ± 0.007^{a}	0.086 ± 0.006^{b}	$p < .05$
Spleen	0.093 ± 0.006^{a}	0.096 ± 0.003^{a}	0.092 ± 0.010^{a}	0.092 ± 0.008^{a}	$p < .05$

[a]Data are reported as mean ± SEM as the ratio of dihomo-gamma-linolenic acid/linoleic acid isolated from membrane phospholipid; $n = 6$ mice/group. Individual one-way ANOVAs with Tukey's *post hoc* tests were used to assess significant differences across the different %en EPA + DHA doses within single tissues (lower case letters). Differences between lower case letters imply significant differences at the $p < .05$ level. The *p*-value column represents the overall *p* value.

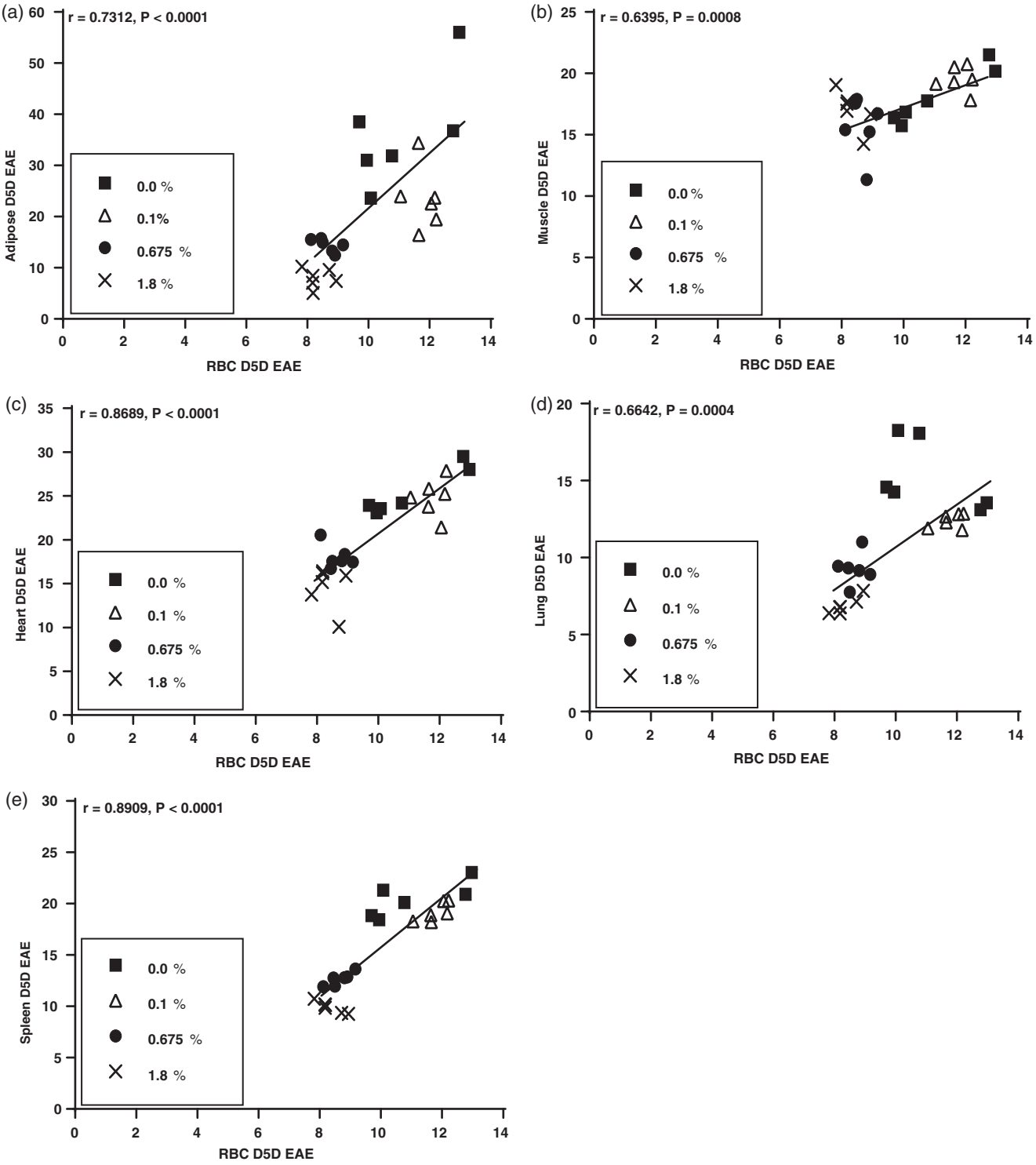

Figure 1. (a)–(e) The correlation between red blood cell (RBC) phospholipid (PL) delta-5 desaturase (D5D) enzymes activity estimates (EAE) and that in adipose (a), muscle (b), heart (c), lung (d) and spleen (e) tissue PL. A Pearson correlation was used to test for linear correlation between the tissues ($n = 24$ per group).

Discussion

In this study, we investigated the relationship between dietary n-3 LCPUFA intake, tissue PL PUFA desaturase EAE and RBC PL PUFA desaturase EAE in non--obese murine models fed diets of increasing %en EPA + DHA. Summaries of our results for D5D and D6D EAE correlations between RBC and tissues, and the effects of increasing EPA + DHA on tissue D5D and D6D EAE are reported in Table 3. Tissue D5D EAE significantly decreased with increasing dietary

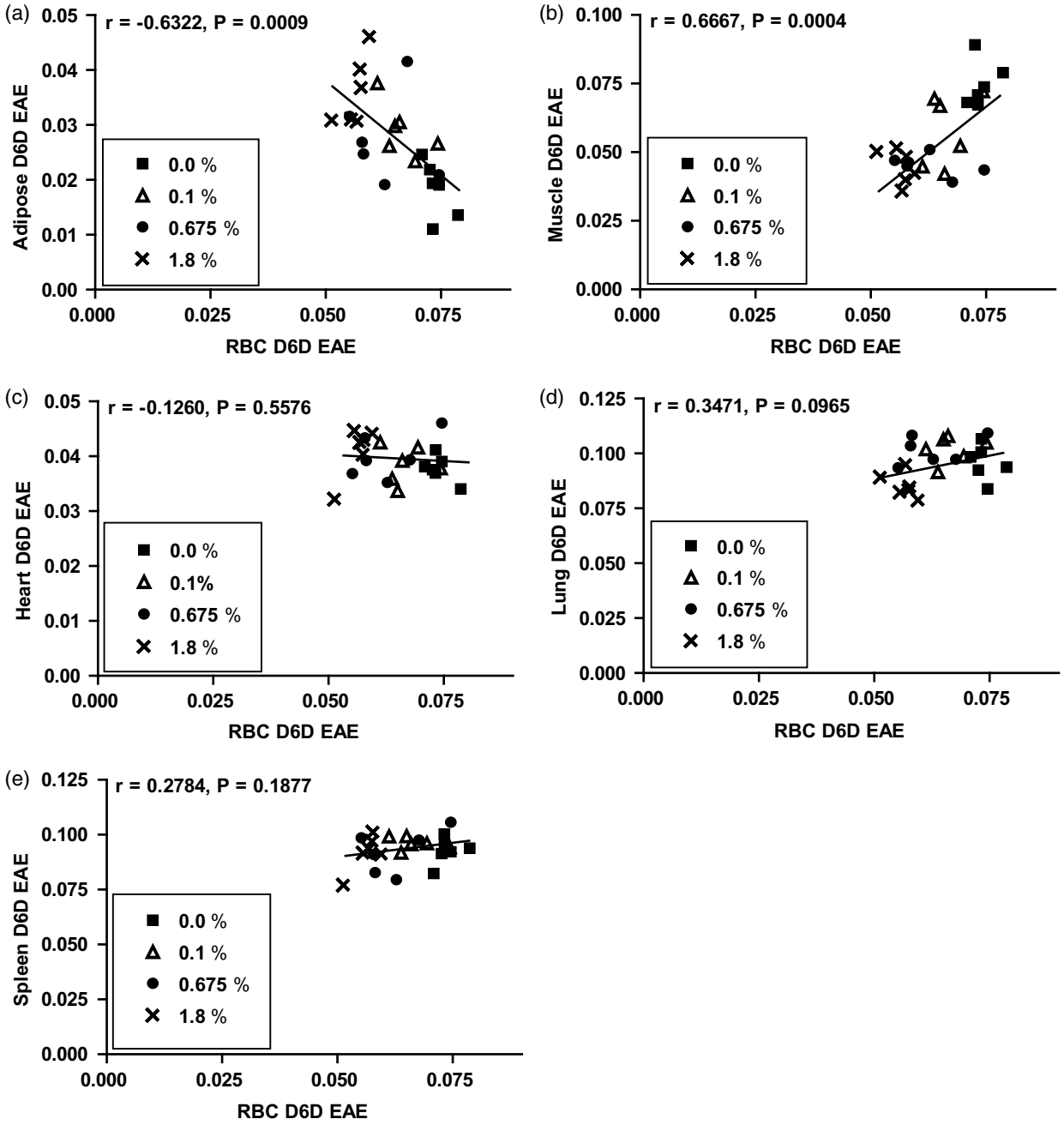

Figure 2. (a)–(e) The correlation between red blood cell (RBC) phospholipid (PL) delta-6 desaturase (D6D) enzyme activity estimates (EAE) and that in adipose (a), muscle (b), heart (c), lung (d) and spleen (e) tissue PL. A Pearson correlation was used to test for linear correlation between the tissues ($n = 24$ per group).

EPA + DHA in adipose, heart, lung and spleen, yet remained unchanged in muscle tissue. Interestingly, tissue D6D EAE did not significantly differ with increasing dietary EPA + DHA. We report RBC D5D EAE were positively correlated with tissue D5D EAE across all tissues, while RBC D6D EAE were correlated with only adipose (negatively) and muscle (positively) tissue PL D6D EAE. Together, these data suggest dietary n-3 LCPUFA EPA + DHA may alter tissue PUFA metabolism through desaturases and that this alteration is reflected by the RBC.

Dietary PUFA modifications and the influence on obesity pathobiology are areas of increasing interest in obesity research. Currently, there are limited reports on the effects of dietary EPA + DHA on tissue-specific D5D and D6D EAE, in non-obese experimental models. Our results suggest tissue D5D EAE significantly decrease in response to increased dietary EPA + DHA.

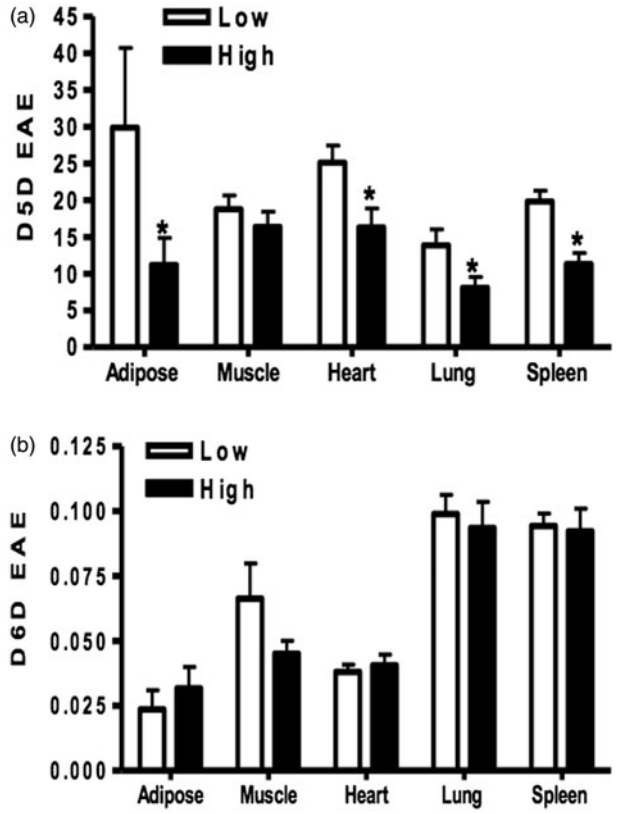

Figure 3. Comparison between delta-5 desaturase (D5D) enzyme activity estimates (EAE) (a) and delta-6 desaturase (D6D) EAE (b) of the lowest treatment groups ((0.0% energy (%en) (eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) and 0.1%en EPA + DHA)) and the highest treatments groups (0.675%en EPA + DHA and 1.8%en EPA + DHA) per specified tissue. A Student's *t*-test was used to assess differences in the tissue-specific D5D EAE and D6D EAE with low and high %en from EPA + DHA. *Denotes a significant difference in D5D EAE between the low ((0.0% energy (%en) (eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) and 0.1%en EPA + DHA)) and high (0.675%en EPA + DHA and 1.8%en EPA + DHA) treatment groups.

Table 3. Summarised results of associations between tissue delta-5 desaturase (D5D) and delta-6 desaturase (D6D) enzyme activity estimates (EAE), estimated red blood cell (RBC) desaturase activities, and increasing dietary eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA)[a].

	RBC	EPA + DHA
Adipose		
D5D	↑	↓
D6D	↓	–
Muscle		
D5D	↑	–
D6D	↑	–
Heart		
D5D	↑	↓
D6D	–	–
Lung		
D5D	↑	↓
D6D	–	–
Spleen		
D5D	↑	↓
D6D	–	–

[a]Individual tissues are bolded. The column titled, "RBC," reports the relationship between tissue and RBC phospholipid (PL) D5D and D6D EAE. ↑ represents a positive and significant correlation; ↓ represents negative and significant correlation, and – represents no significant correlation. A Pearson correlation was used to test for significance, which was established at a $p < .05$. The column titled, "EPA + DHA," reports the relationship between tissue PL D5D and D6D EAE and increasing dietary EPA + DHA. ↓ represents a significant decrease in desaturase activity with increasing dietary EPA + DHA, – represents no change. A Student's *t*-test was used to test for significance which was established at a $p < .05$.

This result was anticipated, since suppression of PUFA desaturase activity by dietary n-3 LCPUFA (i.e. EPA and DHA) is well documented (Brenner & Peluffo 1967; Cho et al. 1999b). Not only do n-3 LCPUFA suppress desaturase activity, but they may also have higher affinity as substrates for desaturase enzymes compared to n-6 PUFA (Patterson et al. 2012). As such, dietary n-3 LCPUFA can inhibit the desaturation of DGLA to ARA, therefore, decreasing ARA content in tissue PL (Gurzell et al. 2014). What remains unclear is whether increased dietary EPA + DHA affects D5D activity by directly inhibiting D5D, displacing n-6 PUFA from D5D, or a combination of inhibition and substrate displacement that results in decreased ARA production. Decreased PL ARA levels are clinically relevant because some ARA oxylipids activate proinflammatory signalling pathways that contribute to chronic low-grade inflammation, obesity and T2D (Robertson 1983; Ricciotti & FitzGerald 2011). Future studies should investigate the biological effects of decreased ARA biosynthesis and PL availability in response to increased dietary consumption of EPA + DHA.

Dysregulated desaturase activity in skeletal muscle is associated with obesity, insulin resistance and altered glucose metabolism (reviewed in detail (Tosi et al. 2014)). Skeletal muscle is rich in the n-6 PUFA, ARA, which is particularly important for skeletal muscle growth and repair (Trappe et al. 2013; Korotkova & Lundberg 2014). ARA accounts for 10–20% of PL FA content in mice (Fenton et al. 2016) and 10% of PL FA content in humans (Andersson et al. 2002). We observed no changes in skeletal muscle D5D EAE in response to increasing dietary EPA + DHA, which may result from high ARA conservation in skeletal muscle. In non-obese mice, inhibition of ARA synthesis by dietary n-3 LCPUFA may not result in significant changes of ARA levels in skeletal muscle PL. Given that D5D EAE is calculated as the ratio of ARA/DGLA, we speculate that the levels of muscle tissue ARA did not change significantly in relation to tissue DGLA levels following increased

dietary EPA + DHA. Therefore, future research should investigate the effect of dietary EPA + DHA on the skeletal muscle desaturases in obesity-associated diseases.

Recent studies have focussed on the link between FA desaturases EAE and diabetes risk (Brenner 1971; Kröger 2012). An increased risk of diabetes is inversely associated with D5D EAE, while increased D6D EAE are positively associated with an increased risk of T2D (reviewed in detail (Kröger 2012)). However, the biological mechanism through which obesity-associated pathology alters desaturases is not well studied. It is suggested that hormonal changes associated with diseases such as T2D modulate desaturase activity (Brenner 2003). Our laboratory recently reported that increased serum C-peptide, a cleaved protein from proinsulin, may inhibit D5D activity independent of obesity and inflammation (Pickens et al. 2016). Changes in membrane PL FA composition attributed to altered D5D and D6D activity may lead to abnormal insulin response in specific tissues, such as the liver (Mercuri et al. 1967). Interestingly, tissue D5D EAE in skeletal muscle did not significantly differ as dietary EPA + DHA increased, even though D5D EAE significantly decreased across all other tissues. Research specific to D5D activity is limited, but given the coordinated activity of D5D and D6D and their common genetic sequences, evidence of tissue-specific D6D expression and activity may be extrapolated to D5D (Cho et al. 1999a). D6D expression and subsequent activity is tissue specific (Brenner 1971; Cho et al. 1999b; Nakamura & Nara 2004). For example, in humans, the expression of D6D is highest in the liver when compared to the brain and other organs (Cho et al. 1999b), while in rats D6D is most active in the liver, but virtually inactive in adipose tissue (Brenner 1971). We suggest future studies characterise D5D expression and activity and confirm whether dietary PUFA intervention affects D5D in the absence of diseases (i.e. obesity).

In summary, these data suggest that increased dietary EPA + DHA intake may differentially affect desaturases in specific tissues. We report that PL RBC desaturases, in particular D5D EAE, are highly correlated with PL tissue desaturases. We acknowledge the need to verify our results in other animal models and non-diseased human populations. Since desaturase EAE have become attractive in disease biomarker discovery, our study provides valuable insight as to how altering EPA + DHA intake affect tissue desaturase EAE in the absence of disease.

Geolocation information

This research was conducted at Michigan State University, East Lansing, MI 48824. Latitude: 42.723642042° 43′ 25.11″ N Longitude:-84.479184084° 28′ 45.06″ W

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Disclosure statement

No potential conflict of interest was reported by the authors.

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