Dietary modulation of oxidized linoleic acid metabolites

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Outline

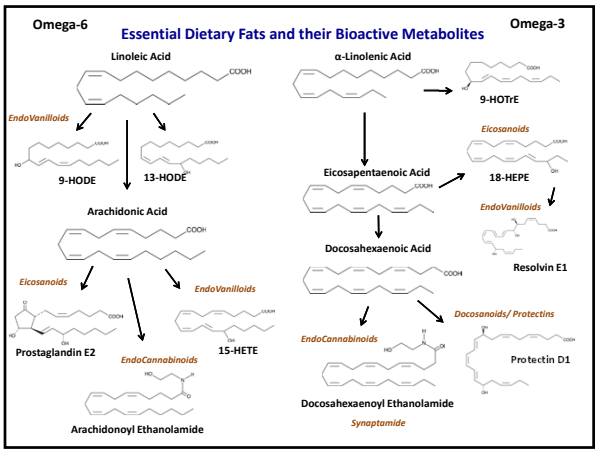
Overview: Fatty acids and their autacoid derivatives

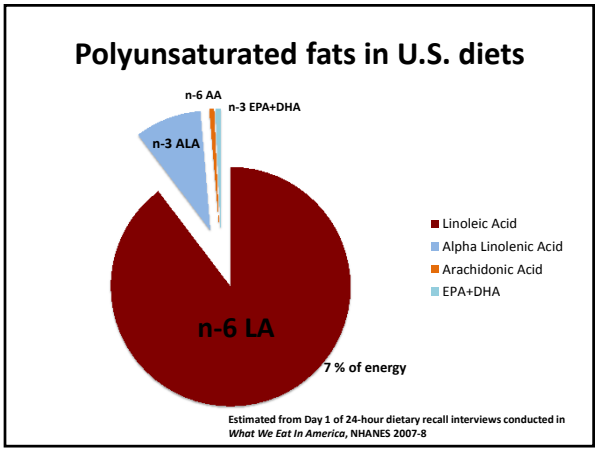
Do dietary n-6 fatty acids play a role in NASH?

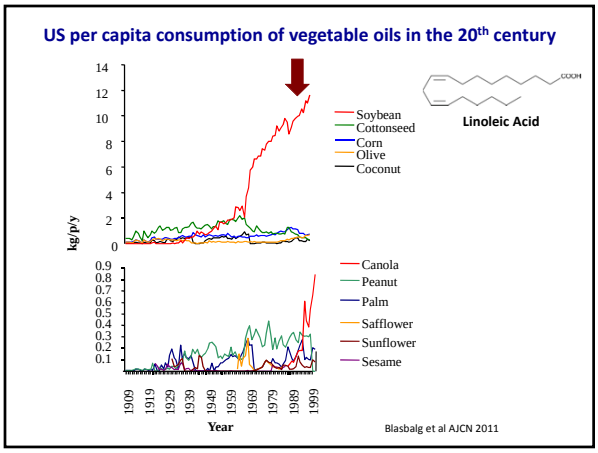
Randomized trial: Targeted alteration of dietary n-3 and n-6 fatty acids for treatment of Chronic Daily Headache

Future Directions

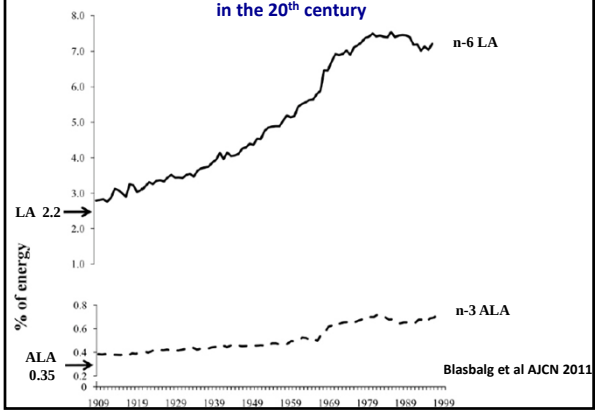
Overview: biochemistry of n-3 and n-6 fatty acids


Omega-6
Essential Dietary Fats and their Bioactive Metabolites
Omega-3
Linoleic Acid
α-Linolenic Acid
9-HOTrE
EndoVanilloids
Eicosanoids
9-HODE
13-HODE
Eicosapentaenoic Acid
18-HEPE
Arachidonic Acid
EndoVanilloids
Docosahexaenoic Acid
Resolvin E1
Eicosanoids
EndoVanilloids
Docosanoids/ Protectins
Prostaglandin E2
15-HETE
EndoCannabinoids
EndoCannabinoids
Protectin D1
Arachidonoyl Ethanolamide
Docosahexaenoyl Ethanolamide
Synaptamide


Polyunsaturated fats in U.S. diets
n-6 AA
n-3 EPA+DHA
n-3 ALA
n-6 LA
7 % of energy
Linoleic Acid
Alpha Linolenic Acid
Arachidonic Acid
EPA+DHA
Estimated from Day 1 of 24-hour dietary recall interviews conducted in
What We Eat In America, NHANES 2007-8


US per capita consumption of vegetable oils in the 20th century
kg/p/y
Soybean
Cottonseed
Corn
Olive
Coconut
Linoleic Acid
Canola
Peanut
Palm
Safflower
Sunflower
Sesame
Year
Blasbalg et al AJCN 2011

US per capita apparent consumption of n-6 LA and n-3 ALA in the 20th century

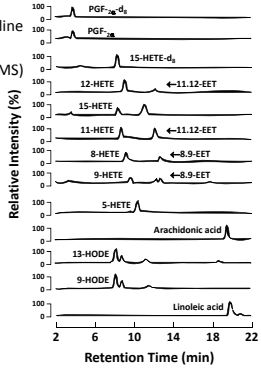


Oxidized linoleic acid in NASH

(Ariel Feldstein et al)

Oxidized Fatty Acid Profiling by Mass Spectrometry

- Liquid chromatography with on-line electrospray ionization tandem mass spectrometry (LC/ESI/MS/MS) and chiral mass spectrometry.
- Quantification specific lipid oxidation products and their stereospecific isomers



Feldstein et al. J. Lipid Res. July 14, 2010

Human Protocol

Clinical suspicion of NAFLD

Baseline → Liver tissue and blood were collected

Stored at -80°C with an antioxidant cocktail in an argon atmosphere

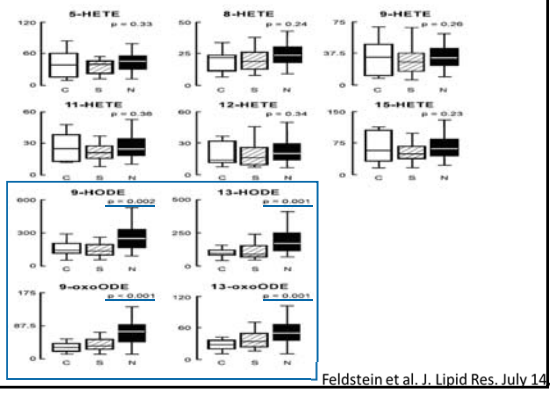
Liver histology (Blinded to OxFA levels)
- Minimal changes (c)
- Isolated steatosis (s)
- NASH (n)

Plasma OxFA levels using LC/ESI/MS/MS (Blinded to liver histology)

OxFA levels compared between three groups of study subjects (n = 73)

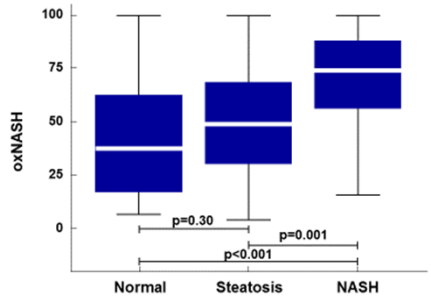
Feldstein et al. J. Lipid Res. July 14, 2010

Circulating OxFA Profile of Human NASH



Feldstein et al. J. Lipid Res. July 14

Correlations Between OxNASH and Pathologist Diagnosis

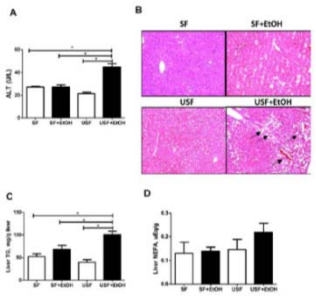


Feldstein et al. J. Lipid Res. July 14, 2010

Dietary linoleic acid in ASH

(Craig McClain et al)

The Type of Dietary Fat Modulates Intestinal Tight Junction Integrity, Gut Permeability, and Hepatic Toll-Like Receptor Expression in a Mouse Model of Alcoholic Liver Disease



Kirpich, McClain et al. Alcohol Clin Exp Res. 2012 May ; 36(5): 835–846.

Dietary modulation of oxidized linoleic acid metabolites

(Ramsden, Feldstein, Mann et al)

PAIN® 154 (2013) 2441–2451

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www.elsevier.com/locate/pain

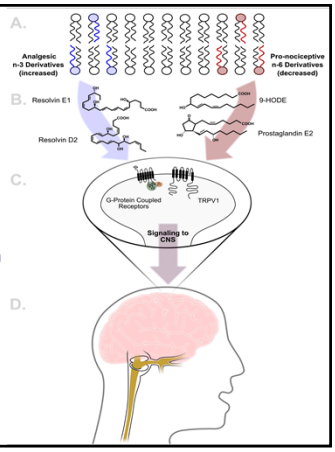
Targeted alteration of dietary n-3 and n-6 fatty acids for the treatment of chronic headaches: A randomized trial

Christopher E. Ramsden [a,b,*], Keturah R. Faurot [b], Daisy Zamora [b], Chirayath M. Suchindran [c], Beth A. MacIntosh [d], Susan Gaylord [b], Amit Ringel [a], Joseph R. Hibbeln [a], Ariel E. Feldstein [e], Trevor A. Mori [f], Anne Barden [f], Chanee Lynch [b], Rebecca Coble [b], Emilie Mas [f], Olafur Palsson [g], David A. Barrow [h], J. Douglas Mann [b,i]

Rationale for targeted dietary intervention

General model

Mechanisms linking n-3 & n-6 fatty acids to physical pain



Development of 2 putative anti-nociceptive dietary interventions

- H3-L6 intervention
  - Increase n-3 EPA and DHA
  - Reduce n-6 LA
- L6 intervention
  - Maintain low n-3 EPA and DHA intakes (typical of US)
  - Reduce n-6 LA and n-6 AA

MacIntosh BA, Ramsden CE et al. *BJN* 2012

LA, EPA and DHA Consumption in Chronic Daily Headache Trial

Intervention	n-6 LA*	n-3 EPA + DHA
Baseline	6.74	46 mg
H3-L6	2.51	1,482 mg
L6	2.40	76 mg

*LA intake is expressed as a percentage of daily food energy (%E). Median intakes assessed via six 24-hour dietary recalls administered on non-consecutive days.

MacIntosh BA, Ramsden CE, Mann JD et al. *BJN* 2012

Chronic Daily Headache Diet Trial

Patient population

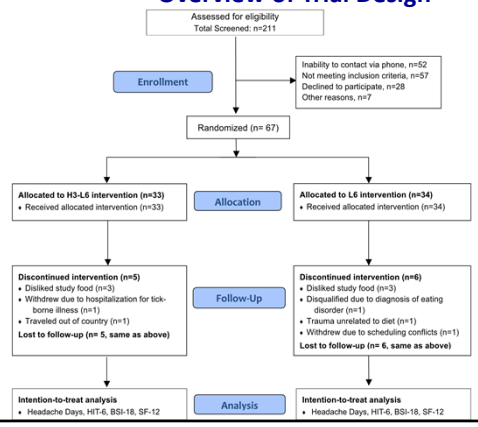
'Chronic Daily Headache'

Headache characteristics

- ≥ 15 headache days per month
- ≥ 4 headache hours per day

Ramsden CE, Faurot K, Hibbeln, JR Mann JD et al., *Trials* 2011

Trial Profile — Overview of Trial Design



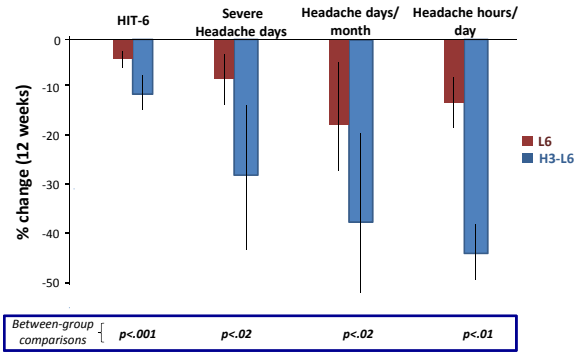
PAIN 2013

Diets altered erythrocyte fatty acids in a manner predicted to reduce physical pain

	H3-L6 Intervention		L6 Intervention		
	% Change (Median)	P-value (Within-group)	% Change (Median)	P-value (Within-group)	P-value (Between-group)
EPA+DHA (n-3 Index)	+97.7	<0.001	+10.8	<0.001	<0.001
n-6 Linoleic acid	-12.1	<0.001	-13.9	<0.001	0.15
n-6 Arachidonic acid	-14.0	<0.001	-7.7	0.53	0.01
n-6 in HUFA score	-21.0	<0.001	-4.0	<0.001	<0.001

Ramsden CE, Mann JD et al., *Trials* 2011, *PAIN* 2013

H3-L6 intervention produced greater pain reduction



Diet-induced changes in anti- and pronociceptive lipid mediators

Diet-induced changes in anti- and pronociceptive lipid mediators

	H3-L6 n=27		L6 n=28		Between-diets
	%change (median)	P value[b]	%change (median)	P value[b]	P value[c]
Anti-nociceptive mediators					
EPA oxidation product					
18-HEPE	+118	<0.001	+61	0.02	<0.001
DHA oxidation products					
17-HDHA	+170	<0.001	+27	0.01	<0.001
RvD2	+39	0.15	+16	0.12	0.60
Pro-nociceptive mediators					
LA oxidation products					
9-HODE	-17	<0.01	-15	0.10	0.35
9-oxoODE	-18	0.05	-12	0.16	0.11
13-oxoODE	-30	<0.01	-19	<0.01	0.35
Total OXLAMs	-18	<0.001	-11	0.02	0.27
AA oxidation products					
5-HETE	-27	0.001	-16	0.10	0.13
8-HETE	-21	0.001	-18	0.02	0.27
9-HETE	-38	<0.001	-23	<0.01	0.24
Total HETEs	-23	0.001	-11	0.04	0.25

Headache Results Summary

The H3-L6 intervention:

Produced statistically significant, clinically relevant improvements in:
- Headache hours per day
- Severe headache days
- Quality of life

Produced marked alterations in circulating n-3 and n-6 derived:
- Eicosanoids
- Resolvin pathway precursors
- Endocannabinoids
- Putative Endovanilloids

Limitations

These findings should be replicated in a larger trial.

Targeted fatty acids were not altered as independent variables.

The clinical effects of the H3-L6 intervention should also be evaluated in comparison to a control **intervention** providing habitual intakes of the targeted dietary fatty acids.

Could not establish whether comparable diet-induced biochemical alterations are possible in other tissues implicated headache pathogenesis

Future directions (NASH)

Determine whether dietary LA lowering:
(1) Reduces OXLAMs in liver
(2) Protects from development/progression NASH

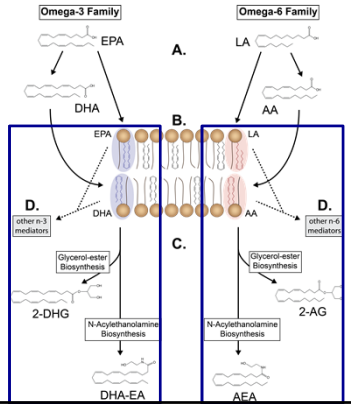
Delineate molecular mechanisms linking dietary LA and OXLAMs to NASH

END

Diet-induced changes in *N*-acylethanolamine and glycerol ester endocannabinoids

Ramsden, Makriyannis, Hibbeln, et al, unpublished

Model depicting diet-induced alterations in endocannabinoids



Diet-induced changes in plasma endocannabinoids

	H3-L6 group [2]				L6 group [2]				Between-group difference p-value[4]
	Baseline	12-weeks	% change	p value[3]	Baseline	12-weeks	% change	p value[3]	
Endocannabinoids (ng/mL)									
n-3 family									
2-DHG	181 (119, 242)	264 (187, 400)	**+65**	<0.001	143 (120, 178)	172 (126, 226)	**+17**	0.14	0.001
DHA-EA	0.43 (0.29, 0.62)	0.80 (0.55, 1.20)	**+99**	<0.001	0.43 (0.29, 0.56)	0.45 (0.37, 0.56)	**+14**	0.43	<0.001
n-6 family									
2-AG	908 (628, 1068)	557 (444, 760)	**-25**	0.001	637 (492, 856)	703 (478, 963)	**+3**	0.50	0.004
AEA	0.49 (0.38, 0.53)	0.44 (0.34, 0.51)	**-3**	0.51	0.47 (0.35, 0.58)	0.50 (0.43, 0.61)	**+1**	0.36	0.059
Other									
OEA	2.74 (2.07, 3.30)	2.71 (2.03, 3.42)	**+9**	0.30	2.82 (2.18, 3.61)	2.83 (2.52, 3.79)	**+13**	0.05	0.408
PEA	3.04 (2.72, 3.63)	3.22 (2.87, 3.87)	**+11**	0.48	3.34 (2.51, 3.91)	3.54 (2.86, 4.38)	**+8**	0.18	0.217
OG	2372 (1584, 3021)	1893 (1429, 2935)	**-7**	0.20	2126 (1771, 2607)	2380 (1703, 2758)	**+8**	0.55	0.265

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END