

University of Groningen

Essential fatty acid absorption and metabolism

Minich, Deanna Marie

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version

Publisher's PDF, also known as Version of record

Publication date:

1999

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Minich, D. M. (1999). Essential fatty acid absorption and metabolism Groningen: s.n.

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Essential Fatty Acid Absorption and Metabolism

RIJKSUNIVERSITEIT GRONINGEN

Essential Fatty Acid Absorption and Metabolism

PROEFSCHRIFT

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. D.F. Bosscher,
in het openbaar te verdedigen op
woensdag 29 september 1999
om 14.15 uur

door

Deanna Marie Minich

geboren op 28 december 1970
te Chicago, Illinois, USA

Promotor

Prof. dr. R.J. Vonk

Co-promotor

Dr. F. Kuipers

Referent

Dr. H.J. Verkade

Promotion Committee Members

Prof. dr. Gerard Hornstra,

DEPARTMENT OF HUMAN BIOLOGY, MAASTRICHT UNIVERSITY

Prof. dr. Peter J.J. Sauer,

BEATRIX KINDERKLINIEK, ACADEMIC HOSPITAL GRONINGEN

Prof. dr. Gerrit L. Scherphof,

DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF GRONINGEN

Paranimfen

Amalia Stamouli

Peter Voshol

Research

This thesis and the research described herein fulfill the requirements necessary to obtain a Doctorate in Medical Sciences from the University of Groningen. Studies were conducted within the Department of Pediatrics, Laboratory of Nutrition and Metabolism, and within the program of the GUIDE research school of the University of Groningen in the Academic Hospital Groningen from 1995-1999.

Copyrights

Permission was granted from the editor for including parts of the article, “Intestinal absorption of essential fatty acids under physiological and essential fatty acid-deficient conditions” (*Journal of Lipid Research* 38:1709-1721, 1997) in Chapter 1 of this thesis.

Funding

The studies presented were made possible by grants from the Netherlands Organization for Scientific Research (NWO) (Grant no. 902-23-097) and by Numico B.V., Zoetermeer, The Netherlands.

Printing of this thesis was financially supported in part by the following:

Solvay Pharmaceuticals, Hannover, Germany

The Dr. Ir. J.H. van der Laar Stichting, Heerlen, The Netherlands

The Dr. Saal van Zwanenbergstichting, Oss, The Netherlands

Friesland Coberco Dairy Foods, R&D-Friesland Nutrition, Leeuwarden, The Netherlands

Glaxo Wellcome B.V., Zeist, The Netherlands

Groningen Institute for Drug Exploration (GUIDE), Groningen, The Netherlands

Janssen-Cilag B.V., Tilburg, The Netherlands

Campro Scientific B.V. and Simac Diagnostica B.V., Veenendaal, The Netherlands

Tramedico B.V., Weesp, The Netherlands

The Nederlandse Vereniging voor Hepatologie, Haarlem, The Netherlands

Hope Farms B.V., Woerden, The Netherlands

UCB Pharma Nederland B.V., Breda, The Netherlands

Advanced Research in Chemistry (ARC), Amsterdam, The Netherlands

Printer

Ponsen & Looijen BV, Wageningen, The Netherlands

Cover design

Deanna

ISBN 90-367-1084-7

“L’essentiel est invisible pour les yeux.”

Le Petit Prince, Antoine de Saint-Exupéry

Acknowledgements

You never know where love will lead you. For me, it was to a little city in the north of the Netherlands which most of my family and friends couldn't even pronounce. After four long years, I can now say that following my heart has had some advantages.

First, I would like to thank my advisors, Henkjan Verkade and Folkert Kuipers, and my professor, Roel Vonk. Henkjan, you have been the most influential person in persuading me to stay in Groningen (another 3 and ½ years longer than I had intended!). You inspired me with your enthusiastic and creative approach to research. Thanks for being a devoted guide during my scientific journey. Folkert, you have been helpful by bringing my perspectives into balance. I am grateful for your quick returns of manuscripts. I will especially remember you for sharing late nights at work and for your familiar, lingering cigar smoke in the hallways. Roel, I appreciate it that you have been very supportive of my work and respectful of my opinions. I have always admired your ability to bring a positive element into our approach to science. Thanks to all of you for giving me the opportunity to experience three different, unique approaches to scientific research.

I want to thank the lab technicians from Kindergeneeskunde for coloring the lab with their spectrum of personalities. Rick, you have participated in almost all of my experiments. Without a doubt, you have done so much for me and I have never heard you complain about it. You are probably one of the most dedicated, perfectionistic (!) technicians I will ever encounter. You have also been there for me as a friend, especially during the last two years. I won't forget our talks (and gossip) during experiments, at the Prinsentuin, and over the operating table about philosophy, relationships, astrology and sports. Renze, thanks for being there to talk about interesting (scientific and non-scientific) issues in the newspaper, to give me advice on personal issues (secrets, secrets) or to consult when everything seemed to be going wrong (extractions, contaminated tubes...). You have also shared much of your gas chromatograph expertise with me. Frans, you have helped me with the technical details in working with stable isotope research and with the desaturase assay. Thanks for sharing your technical knowledge and giving me useful advice. Henk, thanks for your help in running countless fatty acid samples on the IRMS and for those occasional non-scientific chats. Mariska, I really enjoyed working with you those two years. We have had a memorable (!) summer of '98 in the lab scraping dirty diapers. Vincent, thanks for your help in analyzing samples for the EFAD experiment. Henk, you have broadened my knowledge of working with microsomes and generously offered help in the lab when I needed it. Juul, thanks for your help in working up some of my radioactive samples. I enjoyed getting to know all of you during those (brief) coffee (and for me, herbal tea) breaks.

I would also like to thank CKCL. Gerrie and Jan, you have both been extremely patient in assisting me with the gas chromatograph, especially in solving those difficult computer problems. Ingrid, you have provided feedback and generous support for my research. I am very

thankful for your help in getting the GC analysis of fatty acids going. Also, thanks for just being there for me to talk about work and life in Groningen. Herman, I appreciate you spending time with me to learn the vitamin A determination. I also enjoyed your amusing conversations.

Of course, I sincerely thank everyone at CDL, especially Jan Elstrodt and Arie Nijmeijer for assisting me in the setup for doing breath tests in mice.

I would also like to thank the people behind the scenes who took care of all the time-consuming administrative tasks. Heleen, you helped me tremendously at the end of my four years, making sure the planning for my promotion ran smoothly. Nelie Schouten and Janny Tjassing, thank you for your efficiency in organizing my stay here.

I thank all of the AIOs, past and present, for putting up with my craziness these last 4 years. Mini, thanks for showing me the ropes. It was difficult to be working so closely on the same research in the beginning, but as always, it worked out perfectly. We were able to give each other a lot of useful tips. Our time in San Francisco was also quite memorable (bathing in mud and sipping Californian wine in the Napa Valley). Peter, I chose you to be my paranimf because you have been with me through it all. I have told you many times that I felt like you were my big brother away from home. I enjoyed those lazy afternoons in the AIO room when we wrestled (or should I say, you pushed me around a bit?). And one of these days, you better buy a calculator of your own! Johan, I enjoyed those late Saturday night lab chats about life and relationships and research and what is essential in life. Your delicious fish dinners will never be forgotten! Good luck with your research and Ellis! Overall, I have had a great time sitting in the AIO room with everyone. Too bad we didn't spend more afternoons spiking our coffee with whiskey and doing bogus character analysis tests (although, then I would have never finished my promotion on time!). Without all of you, I probably would have never experienced a stripper (space party) or learned nasty Dutch words. We had fun go-karting, running in Lauwersloop (I barely made it!), and playing lasertag and volleyball. Our lunchtime talks about past lives (no, not everyone was Napolean), vertical-swimming fish and 'typical' American behavior were deliciously interesting as well as fun...Torsten, you have taught me that German men do have manners (thanks for the spoon!) and are capable of eating the most synthetic-looking desserts. And the sneak previews on Tuesday night...

Finally, a great, gushy **THANKS** to my family and friends, spread throughout the U.S. and in the Netherlands. What would I have done without e-mail? Amalia, I am so glad that we met and that you agreed to be my paranimf. I will miss our chats in the cafe, and, of course, Hendrik-Jan's advice being shouted through the phone. Thanks Dad for sending those uplifting, midnight e-mails and doing things for me at lightning speed (i.e., transcripts). I wonder if you will now retire since I am finishing my Ph.D. (that's what you promised, right?). Mom, thanks for those occasional Sunday night 2 hour phone chats and for remembering me with cards around the holidays. Bren and Ian - you guys are great! Bren, you have always been my silent supporter and if it weren't for you, I may have turned back and returned to Chicago long time ago. Ian, your e-mails kept me laughing the whole time. Going to Egypt with you has really changed me.

I think we will never forget that experience (shouting at taxi drivers, being stranded in the desert...). Next time, it's Thailand. Tom, thanks for surprising me with those early morning phonecalls. I missed you unbelievably. I told you I would come back, didn't I? Laurie, Agnes, Margaret, Ketan, Tibor, Stephania, Erik, Taco, Klaas, Maya, Shonai, Elaine, Michelle and the rest...thanks for in some way or another, making these last four years an enriching, bearable experience. Spider...thanks for being there with me to dream, to watch the stars and to share our obsession with poetic words...'in between the moon and you, the angels get a better view of the crumbling difference between wrong and right'.

Everyone, thanks for your tremendous support and for lending an ear during those tender times!

In the end, we all learn that home is where the heart is...

Deanna

Groningen, July 1999

TABLE OF CONTENTS

Chapter 1	Introduction	1
	<i>(Parts have been published in Journal of Lipid Research 38:1709-1721, 1997)</i>	2
	1.1 Importance of essential fatty acids	4
	1.2 Essential fatty acid status	8
	1.3 Intestinal absorption of (essential) fatty acids	15
	1.4 Malabsorption of (essential) fatty acids	18
	1.5 Conditions of impaired essential fatty acid status associated with hepatobiliary disturbances	20
	1.6 Scope of this thesis	21
	1.7 Models of altered bile flow and secretion	
Chapter 2	Decreased linoleic acid concentration in the bile-diverted rat is not due to decreased uptake of dietary linoleic acid <i>(Biochimica et Biophysica Acta 1438(1):111-119; 1999)</i>	33
Chapter 3	Decreased net uptake in the intestine and unchanged desaturation and elongation of linoleic acid in a rat model of acute cholestasis <i>(Submitted)</i>	47
Chapter 4	Biliary phospholipid secretion is not required for intestinal absorption and plasma status of linoleic acid in mice <i>(Biochimica et Biophysica Acta, in press)</i>	61
Chapter 5	Impaired postprandial chylomicron formation but quantitatively unaffected fat absorption in multidrug resistance 2 P-glycoprotein-deficient mice <i>(Submitted)</i>	75
Chapter 6	Lipid malabsorption in essential fatty acid-deficient mice is not due to impaired bile secretion <i>(Submitted)</i>	91
Chapter 7	Fat malabsorption in cystic fibrosis patients on enzyme replacement therapy is due to impaired intestinal uptake of long-chain fatty acids <i>(American Journal of Clinical Nutrition 69:127-134, 1999)</i>	105
Chapter 8	General Summary	121
	Nederlandse samenvatting	127
	Summary for non-biologists	131

List of frequently used abbreviations*

AA	Arachidonic acid, 20:4n-6
ADA	Adrenic acid, 22:4n-6
ALA	Alpha-linolenic acid, 18:3n-3
BSSL	Bile salt stimulated lipase
CF	Cystic fibrosis
DAG	Diacylglycerol
DGLA	Dihomo-gamma-linolenic acid, 18:3n-6
DHA	Docosahexaenoic acid, 22:6n-3
DPA	Docosapentaenoic acid, 20:5n-3
EFA	Essential fatty acid
EFAD	Essential fatty acid deficiency
EPA	Eicosapentaenoic acid, 20:5n-3
FABP	Fatty acid binding protein
FFA	Free fatty acid
GLA	Gamma-linolenic acid, 18:3n-6
IFABP	Intestinal fatty acid binding protein
LA	Linoleic acid, 18:2n-6
LCPUFA	Long chain polyunsaturated fatty acid
LDL	Low-density lipoprotein
LFABP	Liver fatty acid binding protein
MA	Mead acid, 20:3n-9
MAG	2-monoacylglycerol
<i>mdr2</i>	Multidrug resistance 2 P-glycoprotein
MTG	Microsomal transfer protein
OA	Oleic acid, 18:1n-9
PA	Palmitic acid, 16:0
PC	Phosphatidylcholine
POA	Palmitoleic acid, 16:1n-7
SA	Stearic acid, 18:0
TAG	Triacylglycerol
TPN	Total parenteral nutrition
VLDL	Very low-density lipoprotein

**Plural forms of the terms listed here are designated in this thesis by the addition of an 's' after the abbreviation.*