The Effect of Dietary Fatty Acid Composition on Skeletal Muscle and Hepatic Fatty Acid and Glucose Metabolism in Male and Female Mice

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COMMON ABBREVIATIONS

A

A	adenine
ACC-α	acetyl-Coenzyme A carboxylase-α
ACC-β	acetyl-Coenzyme A carboxylase-β
Ad libitum	to any desired extent
AICAR	5-aminoimidzole-4-carboxamide-riboside
ALA	α-linoleic acid
AMP	adenosine monophosphate
AMPKα1	AMP-activated protein kinase catalytic subunit α1
AMPKα2	AMP-activated protein kinase catalytic subunit α2
ANOVA	analysis of variance
ATGL	adipose triglyceride lipase
ATP	adenosine triphosphate
ATPase	adenosine triphosphatase
AU	arbitrary units

B

BMI	body mass index
bp	base pairs

C

C	control diet (standard laboratory diet)
C	cytosine
cDNA	complimentary deoxyribonucleic acid
cm	centimetres
CPT1a	carnitine palmitoyl transferase 1a
CPT1b	carnitine palmitoyl transferase 1b
CoA	coenzyme A

D

DAG	diacylglycerol
DGAT	diacylglycerol acyltransferase
DHA	docosahexaenoic acid
DIO	diet-induced obesity
DNA	deoxyribonucleic acid
DPA	docosapentaenoic acid

E

EDL	extensor digitorum longus muscle
EDTA	ethylenediaminetetraacetic acid
ELISA	enzyme linked immunosorbent assay
EPA	eicosapentaenoic acid

F

F	female
FA	fatty acid
FABPpm	fatty acid binding protein
$FADH_2$	flavin adenine dinucleotide (reduced form)
FAS	fatty acid synthase
FAT/CD36	fatty acid translocase
FATP1	fatty acid transport protein 1
FATP2	fatty acid transport protein 2
FATP4	fatty acid transport protein 4
FATP5	fatty acid transport protein 5
FG	fast-twitch glycolytic
FOG	fast-twitch oxidative-glycolytic
FSANZ	Food Standards Australia New Zealand

G

g	grams
G	guanine
GAST LAT	gastrocnemius lateralis
GAST MED	gastrocnemius medialis
GCK	glucokinase
GLUT	glucose transporter
GYS1	glycogen synthase 1
GYS2	glycogen synthase 2

H

H&E	haematoxylin and eosin
HFD	high fat diet
HF-n-3	high fat n-3 polyunsaturated fatty acid enriched diet
HF-S	high saturated fat diet
HK2	hexokinase 2
HSL	hormone sensitive lipase
Hz	hertz

I

IMM	inner mitochondrial membrane
INSIG1	insulin induced gene 1
In situ	in the place where it occurs
IRS	insulin receptor substrate

J

JAK/STAT	Janus kinase/signal transducer and activation of transcription

K

kg	kilograms

L

L	litre
LACS	long chain acyl-CoA synthetase

M

M	moles per litre
M	male
mg	milligrams
MJ	megajoules
mL	millilitres
mm	millimetres
mM	millimoles per litre
mmol/L	millimoles per litre
mol/L	moles per litre
mRNA	messenger ribonucleic acid
MUFA	monounsaturated fatty acid

N

NADH	nicotinamide adenine dinucleotide (reduced form)
NADH-TR	NADH tetrazolium reductase
NADP, NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	non-alcoholic fatty liver disease
ng	nanograms
NHMRC	National Health and Medical Research Council
nm	nanometres
nM	nanomoles per litre

O

OD	optical density
OMM	outer mitochondrial membrane

P

PAS	periodic acid-Schiff
PCR	polymerase chain reaction
PDK4	pyruvate dehydrogenase kinase 4
PDPK1	3-phosphoinositide-dependent protein kinase 1
PEPCK	phosphoenolpyruvate carboxykinase
PFK-L	phosphofructokinase - liver isoform
PFK-M	phosphofructokinase - muscle isoform
PGC1α	peroxisome proliferative activated receptor γ coactivator 1α
PI3Kr1	phosphatidylinositol 3-kinase, regulatory subunit, polypeptide 1
PIP2	phosphoinositol-4,5-bisphosphate
PIP3	phosphoinositol-3,4,5-triphosphate
PKB	protein kinase B
PKC	protein kinase C
PLAN	plantaris muscle
pmol/L	picomoles per litre
POLR2c	RNA Polymerase 2c
PPARα	peroxisome proliferator activator receptor α
PPARδ/β	peroxisome proliferator activator receptor δ/β
PPARγ	peroxisome proliferator activator receptor γ
PPRE	peroxisome proliferator activator receptor response element
PUFA	polyunsaturated fatty acid

Q, R

r	pearson correlation coefficient
RECT FEM	rectus femoris muscle
RNA	ribonucleic acid
RPLP0	large ribosomal protein P0
rpm	revolutions per minute
rfu	relative fluorescence units

S

S1P	site-1 protease
S2P	site-2 protease
SCAP	SREBP cleavage-activating protein
SCD1	stearoyl-Coenzyme A desaturase 1
SDH	succinic dehydrogenase
SEM	standard error of the mean
SFA	saturated fatty acid
SIRT1	sirtuin 1
SLC27	solute carrier family 27
SO	slow-twitch oxidative
SOCS3	suppressor of cytokine signalling 3
SOL	soleus muscle
SPSS	statistical package for social scientists
SREBF1	sterol regulatory element binding transcription factor 1

T

T	tyrosine
TBP	TATA-binding protein
TG	triglyceride
TGH	triglyceride hydrolase
TIB	tibalis muscle
TMB	tetramethylbenzidine

U

UCP2	uncoupling protein 2
UCP3	uncoupling protein 3
U/mL	units per millilitre

V, W, X, Y

VAST INT	vastus lateralis intermedius
VAST LAT	vastus lateralis muscle
VAST MED	vastus medialis muscle
ver.	version

Z

ZDF	obese insulin resistant Zucker rat

Symbols

°C	degrees Celcius
µg	micrograms
µl	microlitres
µm	micrometres
≤	less than or equal to
>	greater than or equal to
~	approximately

ABSTRACT

Australian adults consume ~6% above the recommended intake of saturated fat and less than half the recommended daily amount of n-3 polyunsaturated fatty acids (PUFA). There is some evidence that the type and proportion of dietary fat consumed may influence the development of the obese phenotype and associated metabolic complications.

Epidemiological studies indicate that a saturated fat-rich diet (HF-S) is deleterious, whilst consuming n-3 PUFAs is beneficial to metabolic health. Saturated fats have a greater propensity to enter storage in adipose tissue and ectopic stores, as opposed to being oxidised. This is deleterious as ectopic fat deposition in skeletal muscle and liver are strongly associated with insulin resistance. In contrast, diets rich in n-3 PUFA limit adipose tissue hypertrophy, reduce ectopic fat and prevent high fat diet (HFD)-induced insulin resistance in rats. However, the mechanism by which n-3 PUFA enrichment of a HF-S diet (HF-n-3) prevents ectopic fat deposition in muscle and liver is unclear; though pathways of fatty acid uptake, storage and oxidation may be implicated. Furthermore, in skeletal muscle a functional shift in fibre type may be implicated, as increased muscle n-3 PUFA content is associated with an increased proportion of oxidative fibres. The studies in this thesis therefore aimed to determine: (I) the effect of HFD fatty acid composition on metabolic profile, adipose tissue distribution, and muscle fibre type composition of male and female mice; (II) if HF-n-3 feeding influenced the mRNA content of 27 key genes that regulate the uptake (FAT/CD36, FABPpm, FATP), synthesis and storage (SREBF, INSIG, SCD, ACC, DGAT, HSL) and utilisation (PDK, PPAR, PGC1, AMPK, ACC, CPT1, UCP) of fatty acids and

metabolism of glucose (HK, PFK, GYS) in the glycolytic extensor digitorum longus muscle, oxidative soleus muscle and liver of male and female mice. To assess these aims mice were fed either a control diet (16% energy from fat) or one of two HFDs (60% energy from fat), a HF-S or HF-n-3 (7.5% saturated fat replaced with n-3 PUFA) diet. I investigated the hypothesis that HF-n-3 feeding prevents ectopic fat deposition through enhanced uptake and utilisation, and reduced storage, of fatty acids.

Despite similarly increased body weight with both HFDs, mesenteric fat mass decreased and brown fat increased with HF-n-3 feeding compared to HF-S feeding. HF-S feeding increased muscle and liver fat content; this was ameliorated by HF-n-3. As hypothesised, HF-n-3 feeding may ameliorate intramyocellular and intrahepatic fat accumulation through an altered pattern of fatty acid metabolism gene expression in those tissues, specifically through the concurrent activation of pathways regulating fatty acid transport and utilisation, whilst limiting pathways that promote fatty acid storage and lipogenesis. Muscle fibre type composition was unchanged with diet, although HF-n-3 feeding increased muscle oxidative capacity. HF-S mice exhibited increased plasma insulin and glucose metabolism was influenced by HF-n-3 feeding in a tissue-specific manner. These studies highlight the importance of gender and in skeletal muscle, muscle fibre type, to the overall characteristics, profile of gene expression and ultimate function of the skeletal muscle and liver.

DECLARATION

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution to Lisa Kate Philp, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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