Nutrition, acides gras et développement de l'adiposité

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- Généralités

- Existence de périodes sensibles au cours de la mise en place du tissu adipeux

- Différenciation adipocytaire et effecteurs hormonaux

- Non-équivalence des acides gras dans le développement du tissu adipeux

- Relations avec l'obésité infantile

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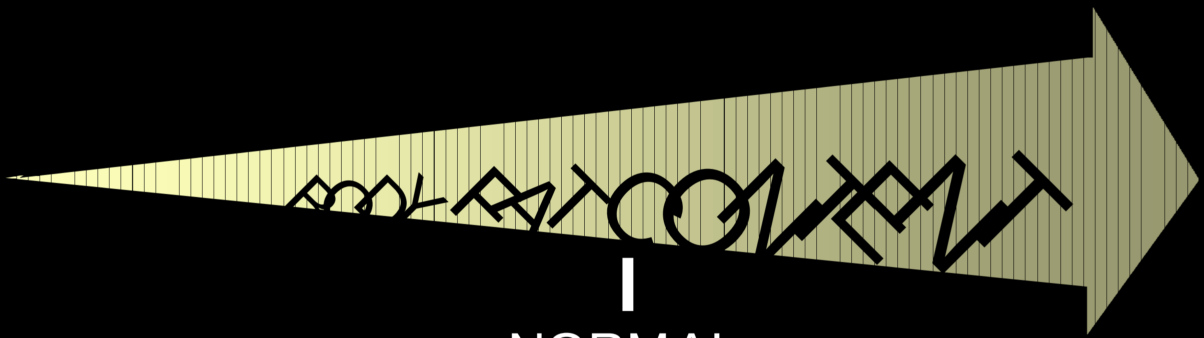
BENEFICIAL EFFECTS OF ADIPOSE TISSUE

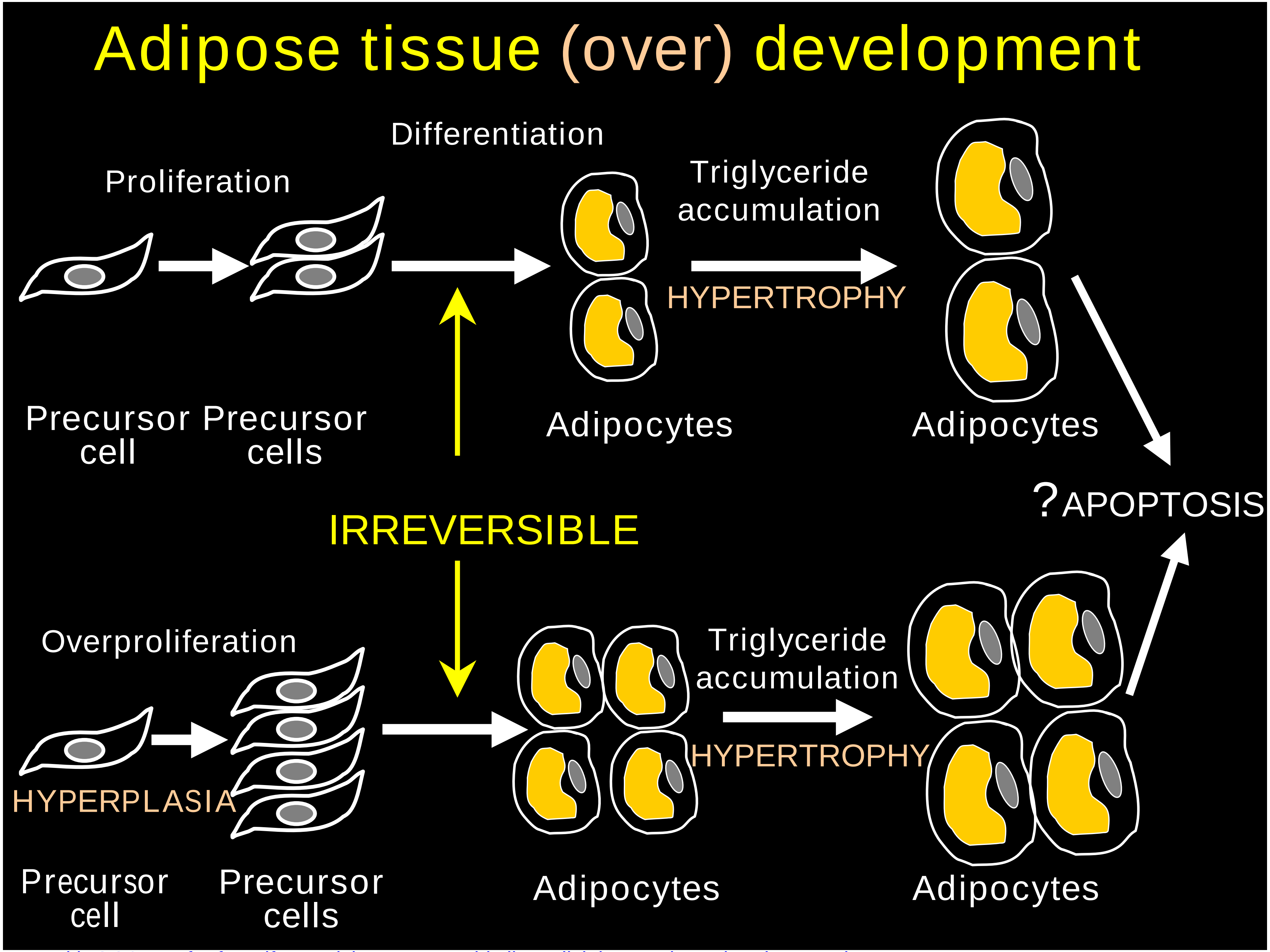
LIPOATROPHY → DIABETES



OBESITY → DIABETES

NORMAL RANGE

- RESISTANCE TO FASTING
- GLUCOSE & FATTY ACID HOMEOSTASIS
- REPRODUCTION


Adipose tissue (over) development
Differentiation
Proliferation
Triglyceride
accumulation
HYPERTROPHY
Precursor
cell
Precursor
cells
Adipocytes
Adipocytes
IRREVERSIBLE
?APOPTOSIS
Overproliferation
Triglyceride
accumulation
HYPERTROPHY
HYPERPLASIA
Precursor
cell
Precursor
cells
Adipocytes
Adipocytes

Développement du Tissu Adipeux

] L 'augmentation de la masse adipeuse fait à la fois intervenir

Hypertrophie

(volume des adipocytes)

Hyperplasie

(nombre des adipocytes)

] L'estimation de la cellularité se limite à mesurer *a posteriori* le nombre et le volume des adipocytes qui cessent de se diviser.

] Ignorance des pools de cellules précurseurs *sans importance pondérale*, présents tout au cours de la vie et donc potentiellement capables de proliférer et de se différencier ultérieurement (véritable mesure du potentiel du développement du tissu adipeux).

Caractérisation *nécessaire* de marqueurs spécifiques des cellules précurseurs d 'adipocytes afin de quantifier la taille de ces pools en fonction du développement et des conditions nutritionnelles.

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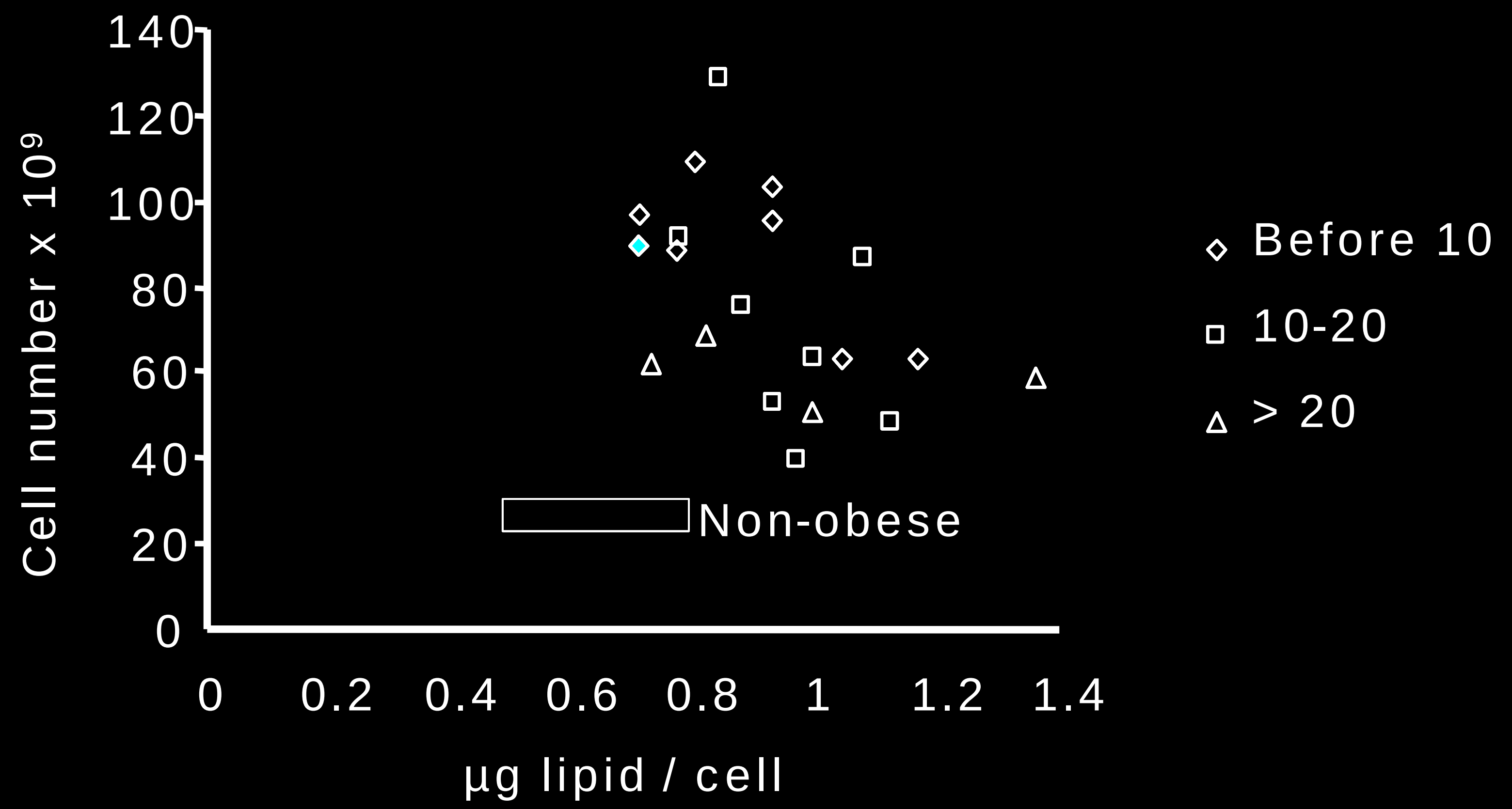
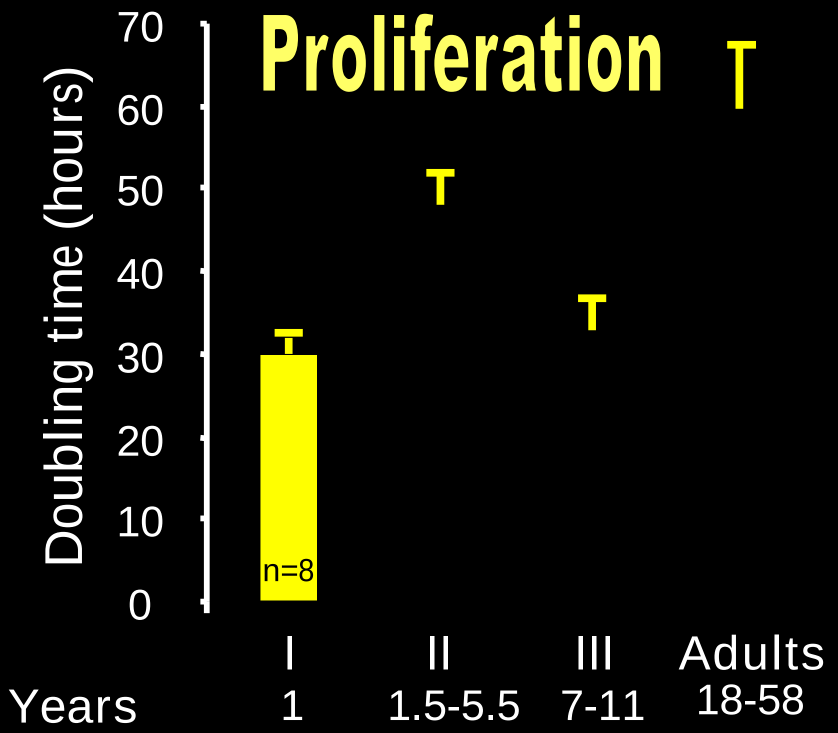
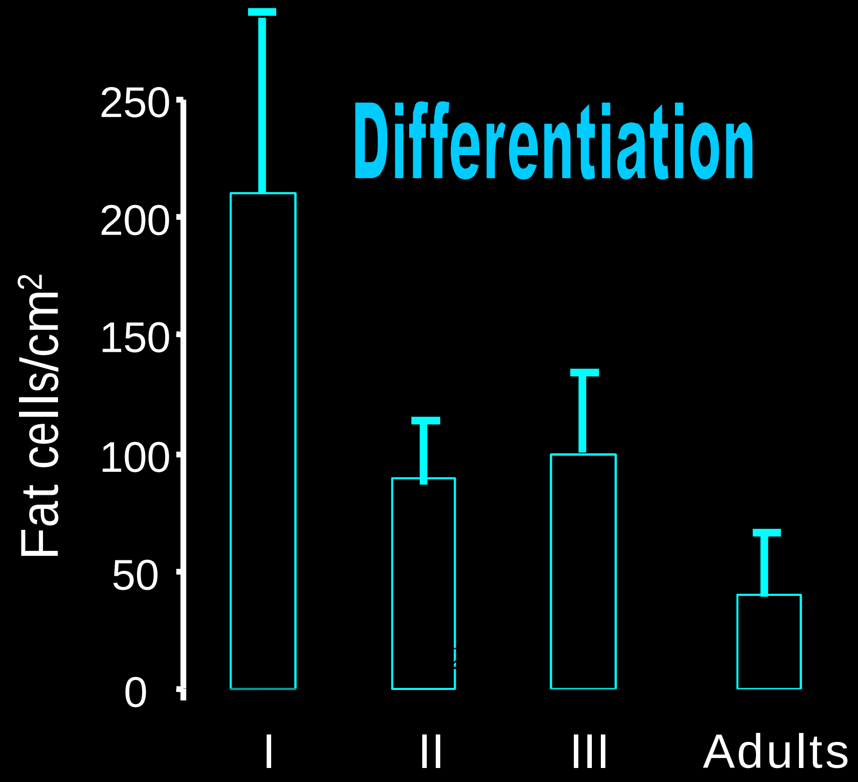
Cellularity of obese patients depends on the age of onset (Knittle JL. et al., 1979)



Effect of donor age on the proliferation and differentiation of human adipose precursor cells (Hauner *et al*., 1988)





Group	BMI	Fat cell size (µm)
I	16.8± 1.0	33.2± 7.5
II	15.1± 1.2	37.3± 8.5
III	15.8± 2.1	43.6± 11.8
Adults	24.5± 1.7	54.1± 10.3

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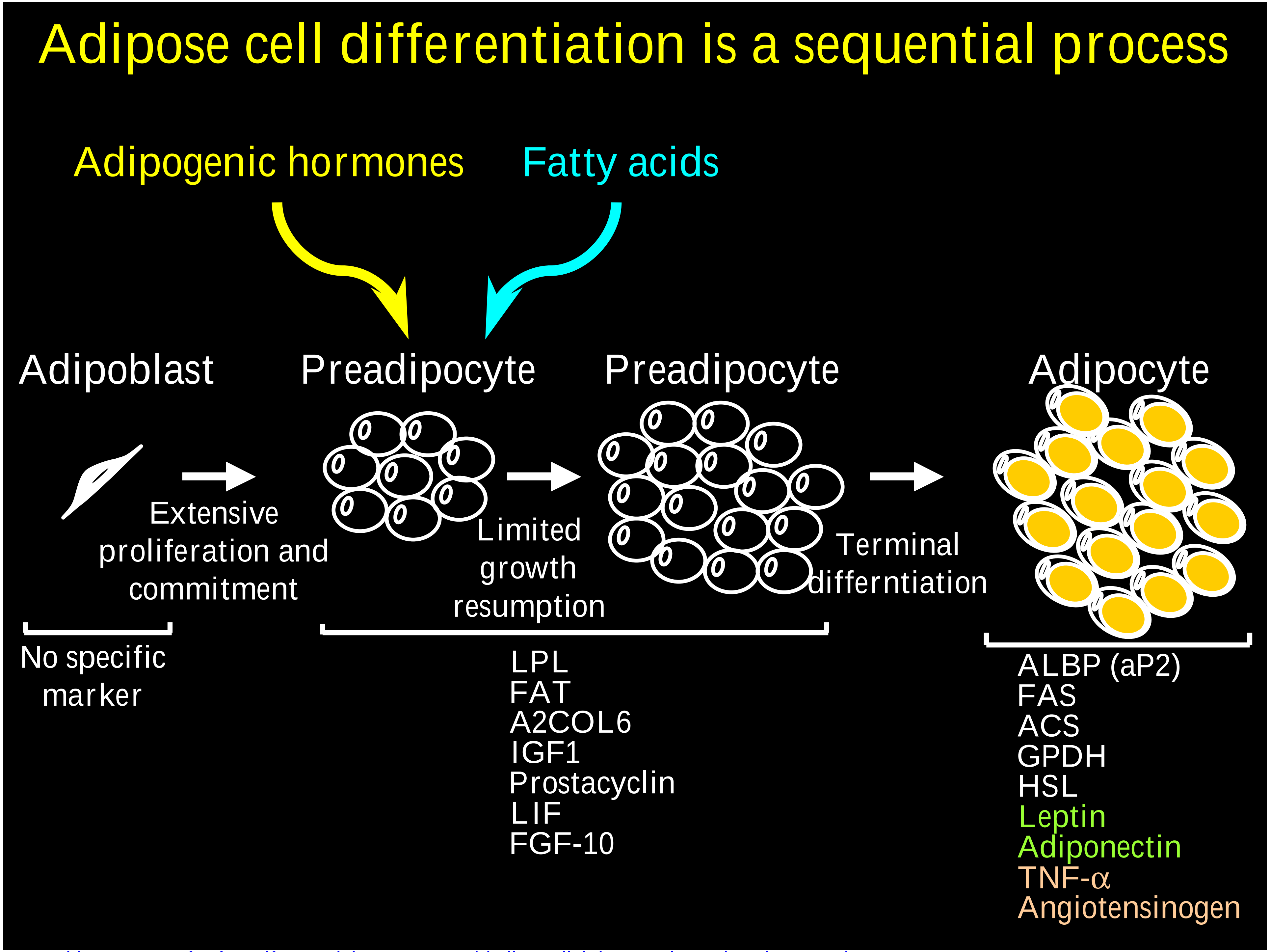
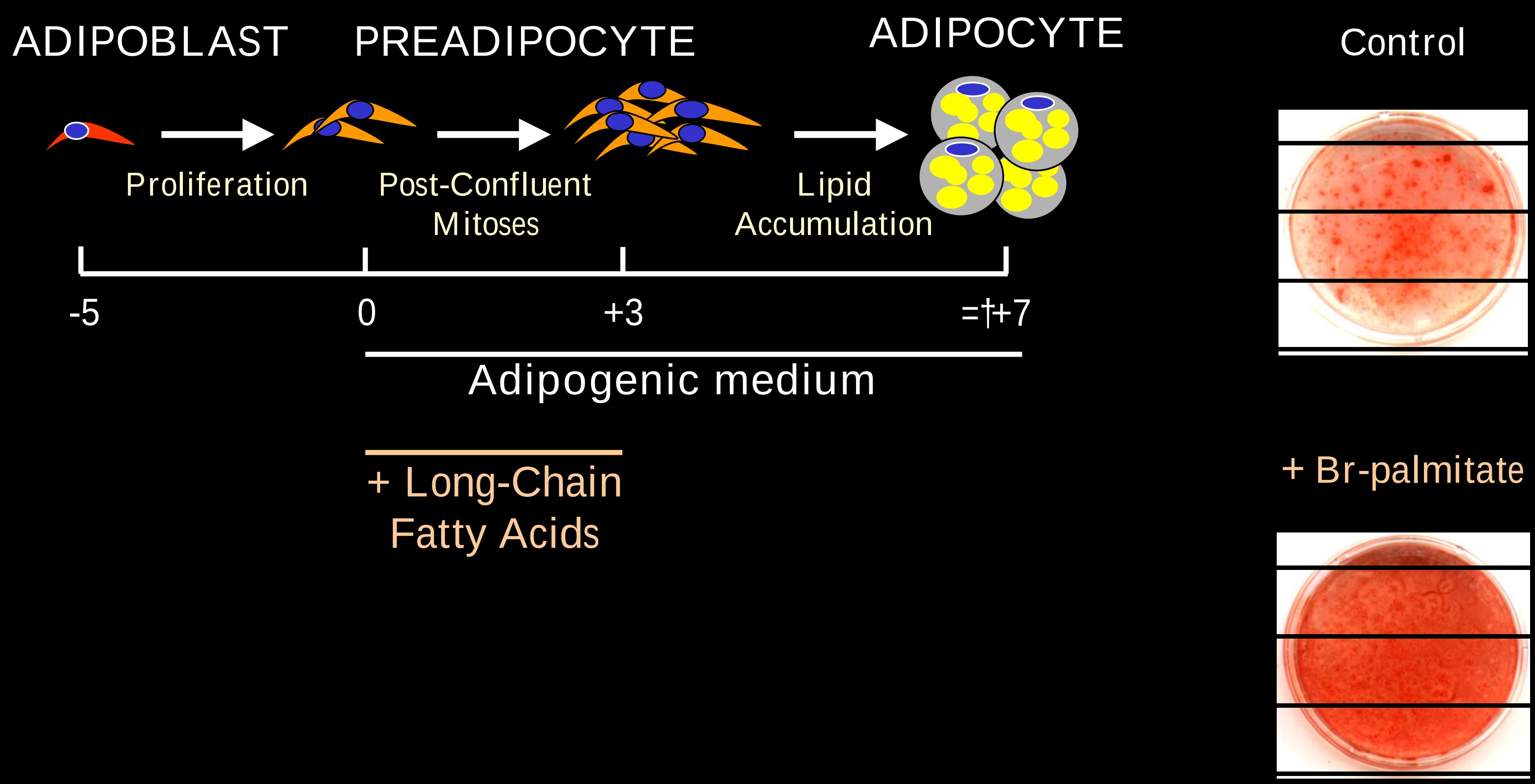

Adipose cell differentiation is a sequential process
Adipogenic hormones
Fatty acids
Adipoblast
Preadipocyte
Preadipocyte
Adipocyte
Extensive proliferation and commitment
Limited growth resumption
Terminal differntiation
No specific marker
LPL
FAT
A2COL6
IGF1
Prostacyclin
LIF
FGF-10
ALBP (aP2)
FAS
ACS
GPDH
HSL
Leptin
Adiponectin
TNF-α
Angiotensinogen

DIETARY FATTY ACIDS PROMOTE ADIPOGENESIS



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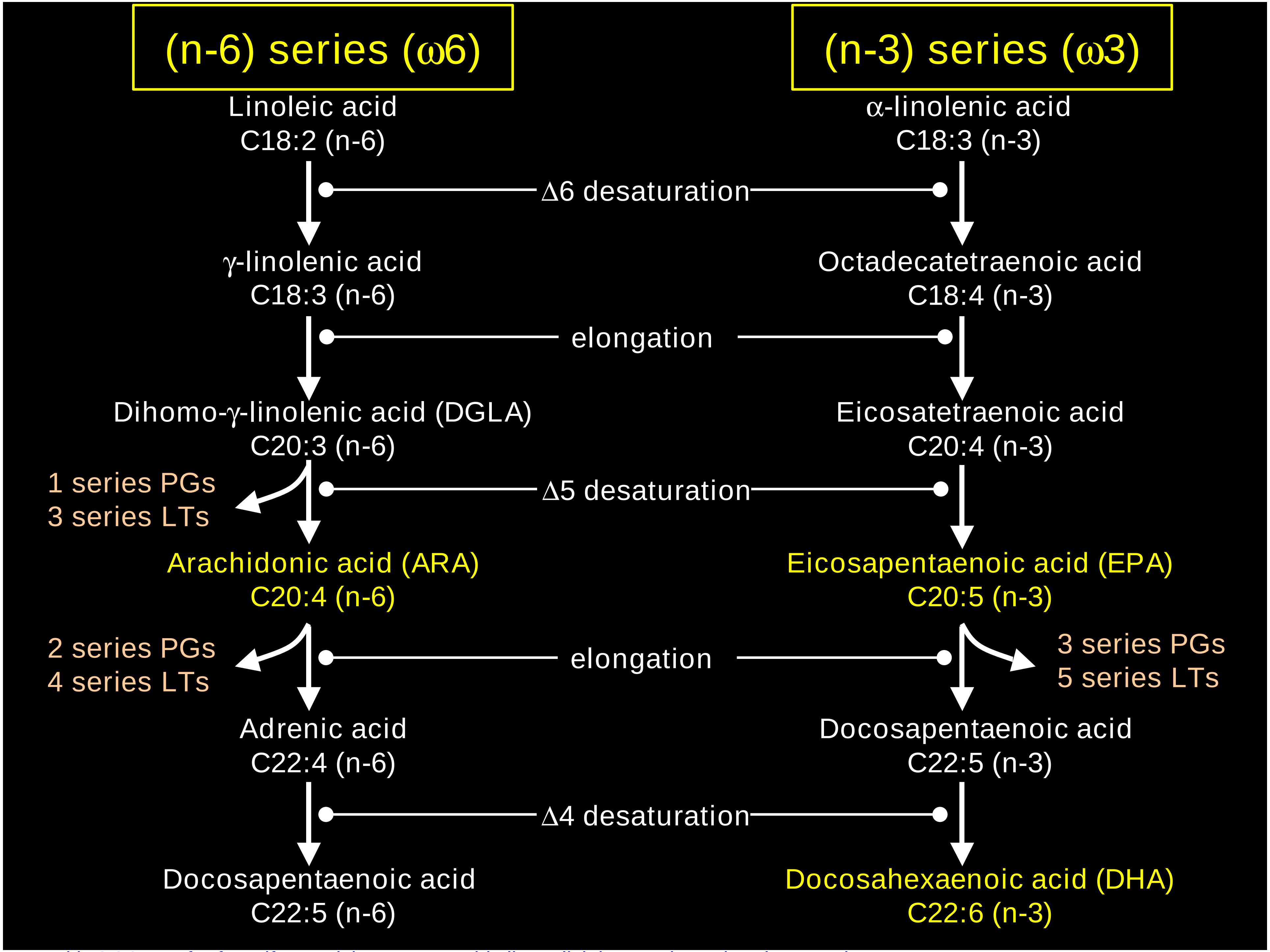
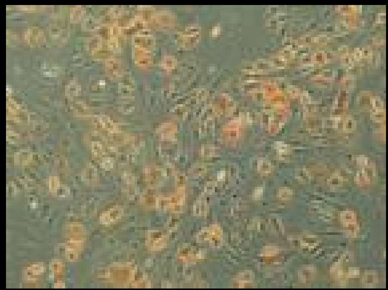


(n-6) series (ω6)
(n-3) series (ω3)
Linoleic acid
C18:2 (n-6)
α-linolenic acid
C18:3 (n-3)
Δ6 desaturation
γ-linolenic acid
C18:3 (n-6)
Octadecatetraenoic acid
C18:4 (n-3)
elongation
Dihomo-γ-linolenic acid (DGLA)
C20:3 (n-6)
Eicosatetraenoic acid
C20:4 (n-3)
1 series PGs
3 series LTs
Δ5 desaturation
Arachidonic acid (ARA)
C20:4 (n-6)
Eicosapentaenoic acid (EPA)
C20:5 (n-3)
2 series PGs
4 series LTs
elongation
3 series PGs
5 series LTs
Adrenic acid
C22:4 (n-6)
Docosapentaenoic acid
C22:5 (n-3)
Δ4 desaturation
Docosapentaenoic acid
C22:5 (n-6)
Docosahexaenoic acid (DHA)
C22:6 (n-3)

Adipogenesis in response to PPAR agonists and long-chain fatty acids

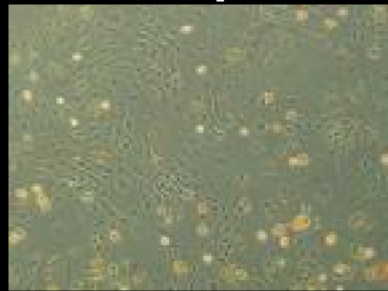
Control

ω6ARA

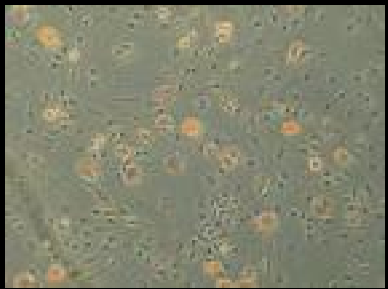


ω3ARA

ω6ARA +aspirin



DHA



cPGI2

δ ag.

δ + γ ag.

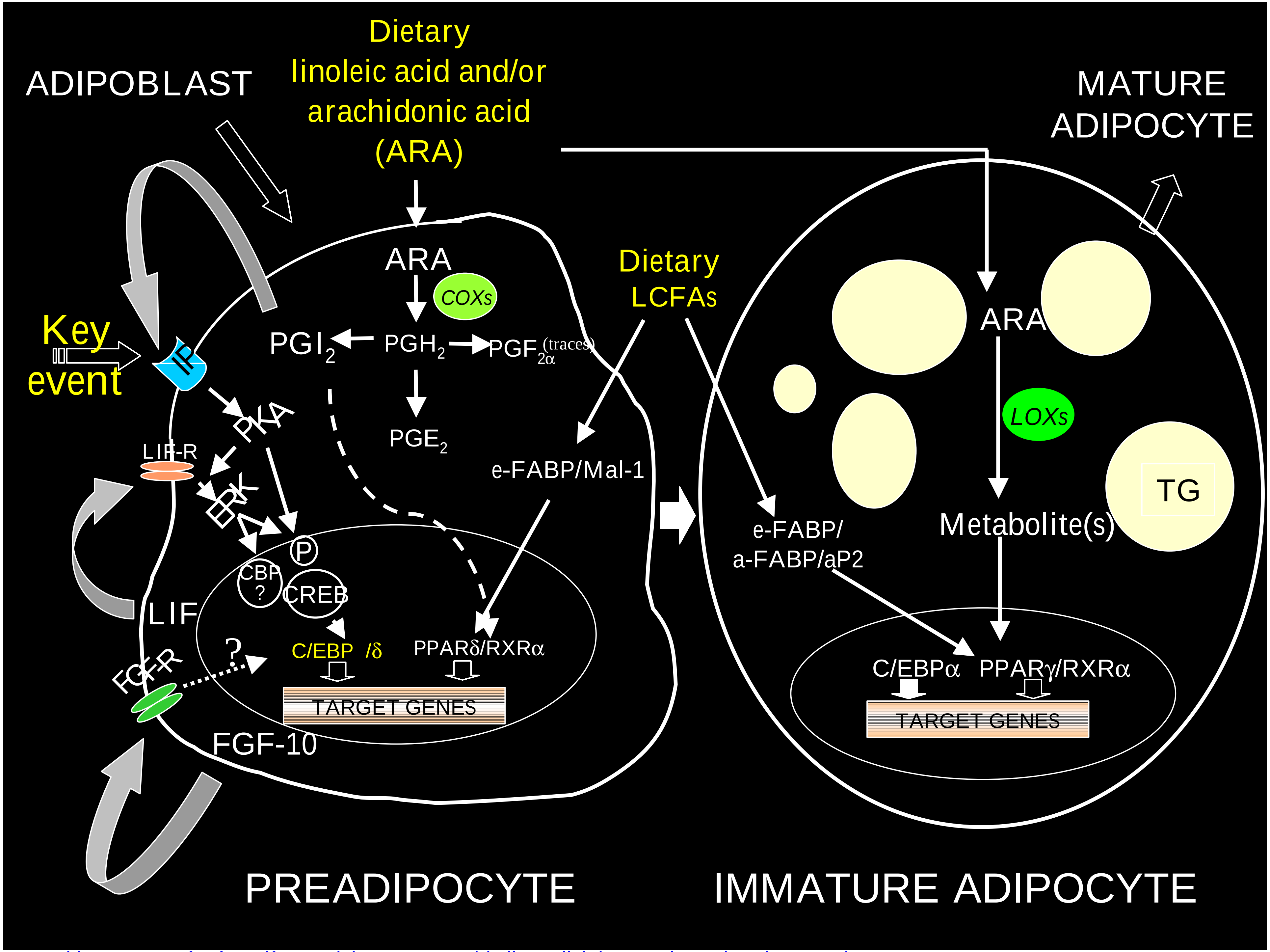
ARACHIDONIC ACID (C20:4 n-6) IS UNIQUE AMONG LONG-CHAIN FATTY ACIDS TO ACT AS A POTENT ADIPOGENIC EFFECTOR

ADDITION FROM DAY 0 TO DAY 3		ADDITION FROM DAY 3 TO DAY 7	GPDH ACTIVITY (fold increase)
None		None	1.0•
δagonist		γ agonist	5.7 ± 1.6
ω-6 arachidonic acid	(10µM)	γ agonist	17.5 ± 6.2**
ω-3 arachidonic acid	(«)	«	5.5 ± 1.2**
Palmitic acid	(«)	«	2.3 ± 0.5*
Pamitoleic acid	(«)	«	3.5 ± 0.8*
Oleic acid	(«)	«	2.2 ± 0.4*
EPA	(5µM)	«	3.5 ± 0.9*
DHA	(5µM)	«	4.1 ± 1.2*
CLA°	(10µM)	«	3.1 ± 0.7
Carbacyclin	(0.2µM)	«	17.3 ± 3.0***

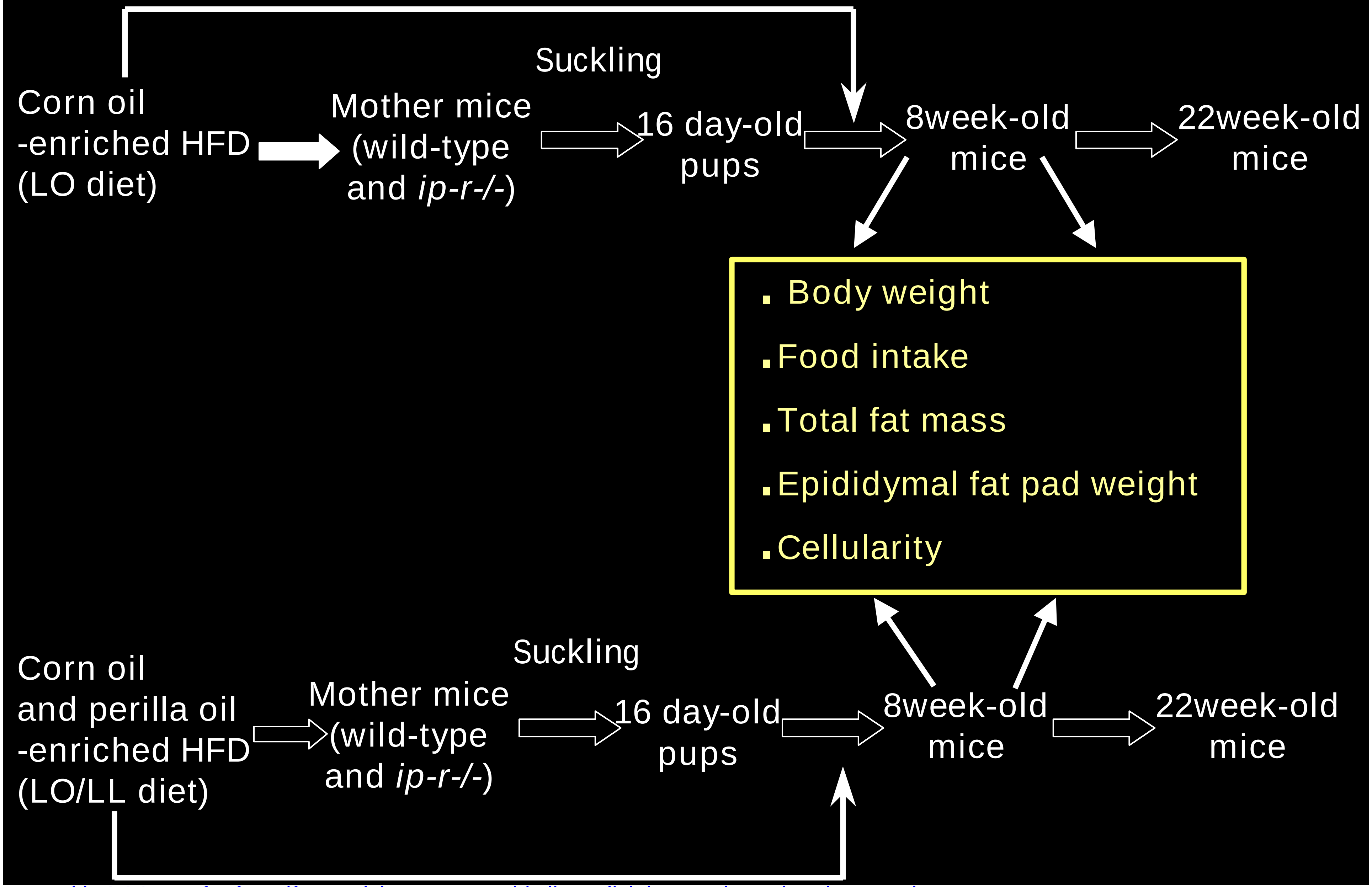
• 30mU/mg of protein; * P<0.01; ** P<0.05 versus untreated cells;*** P<0.01 versus untreated cells; γ agonist, BRL49653 (0.5µM); ° CLA (10E, 12Z)

• PARMI LES ACIDES GRAS A LONGUE CHAINE, L 'ACIDE ARACHIDONIQUE $\omega 6$ SE REVELE SEUL CAPABLE DE STIMULER LA PRODUCTION D'AMPc ET LA VOIE PKA via LA PRODUCTION ET LA SECRETION DE PROSTACYCLINE, QUI SE LIE AU RECEPTEUR DE SURFACE IP-R.

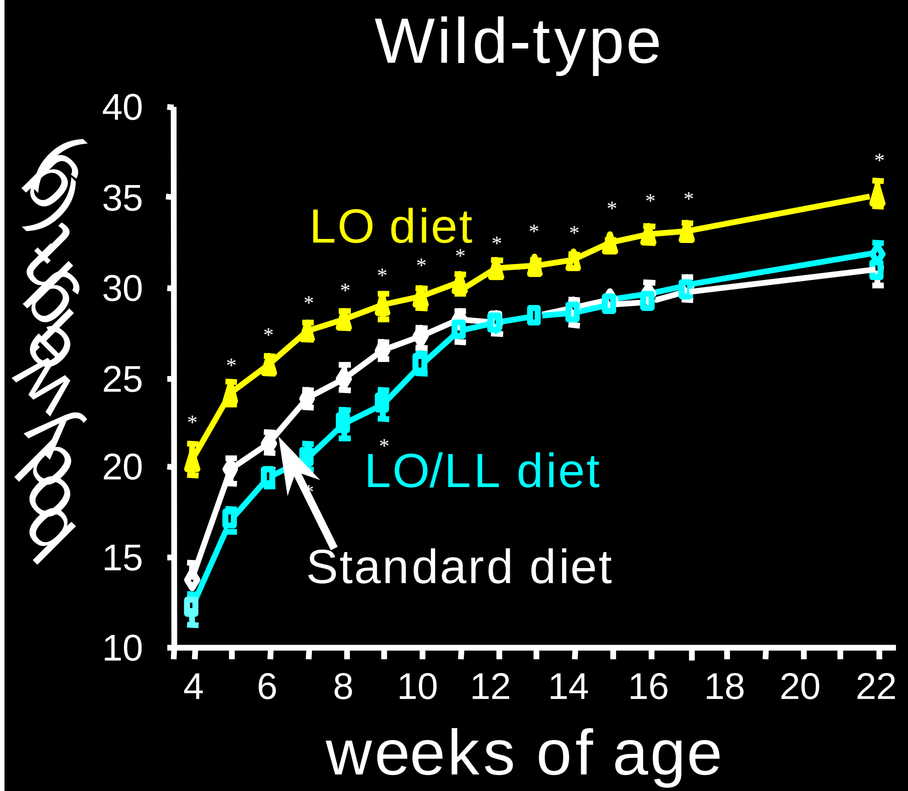
• LES ACIDES GRAS DE LA SERIE $\omega 3$ (EPA > DHA) INHIBENT LA PRODUCTION D 'AMPc STIMULEE PAR L 'ACIDE ARACHIDONIQUE.

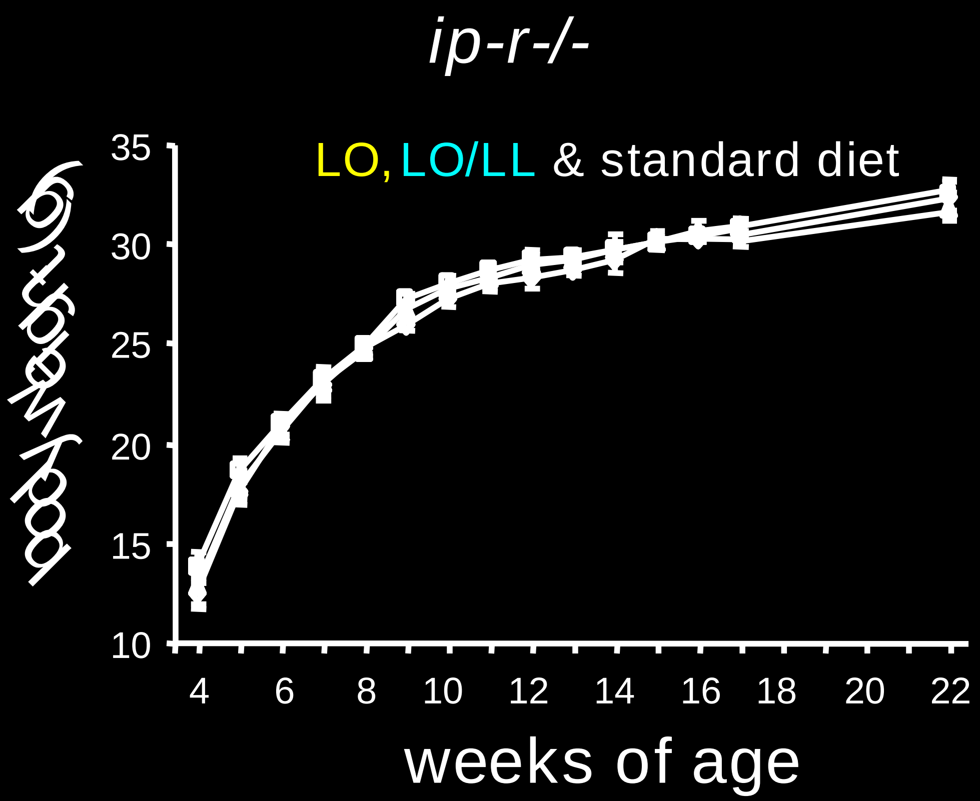

ADIPOBLAST
Dietary
linoleic acid and/or
arachidonic acid
(ARA)
MATURE
ADIPOCYTE
ARA
COXs
Dietary
LCFAs
ARA
Key
event
IP
PGI2
PGH2
PGF2α (traces)
PKA
LOXs
PGE2
LIF-R
e-FABP/Mal-1
ERK
e-FABP/
a-FABP/aP2
Metabolite(s)
TG
P
CBP
?
CREB
LIF
?
C/EBP /δ
PPARδ/RXRα
C/EBPα
PPARγ/RXRα
FGF-R
TARGET GENES
TARGET GENES
FGF-10
PREADIPOCYTE
IMMATURE ADIPOCYTE

Dietary fatty acids and WAT development



Body weight of wild-type and *ip-r-/-* male mice





- COMPARATIVE RESULTS OBTAINED WITH WILD-TYPE AND TRANSGENIC MICE SHOW THAT POLYUNSATURATED FATTY ACIDS OF THE ω-6 AND ω-3 SERIES ARE *NOT* EQUIPOTENT IN PROMOTING THE FORMATION OF ADIPOCYTES *IN VITRO* AND ADIPOSE TISSUE DEVELOPMENT *IN VIVO* (LINOLEIC ACID> αLINOLENIC ACID)

- THE PREGNANCY-LACTATION PERIOD APPEARS CRITICAL TO OBSERVE A SIGNIFICANT ENHANCEMENT OF ADIPOSE TISSUE MASS BY LINOLEIC-ENRICHED DIET

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ω6 Linoleate and ω3 α-Linolenate as essential polyunsaturated fatty acids (PUFAs)

- Because of the concomitant absence of dietary α-linolenate, essential PUFA deficiency is a seriously flawed model that has probably *led to significantly overestimating linoleate requirement*

Linoleate requirement during pregnancy, lactation and early development is thought *not to exceed 3% of total energy intake* (0.5-1.5% in adults as compared to 7% actually observed) (S.C. Cunnane, 2003)

- Today, the ω6/ω3 ratio in foods varies between 10 and 40 whereas, *during evolution*, it was 1 or even less. The typical Greek-Crete diet is closer to the ''Paleolithic'' diet that the current Western diets (A.P. Simopoulos, 1999)

FAT INTAKE and WAT DEVELOPMENT DURING CHILDHOOD

Pro

High-fat intake associated with a gain of fat mass in children

Con

Lack of evidence of a general increase in energy intake as fat among youths despite a striking increase in the prevalence of overweight and obesity

Answers

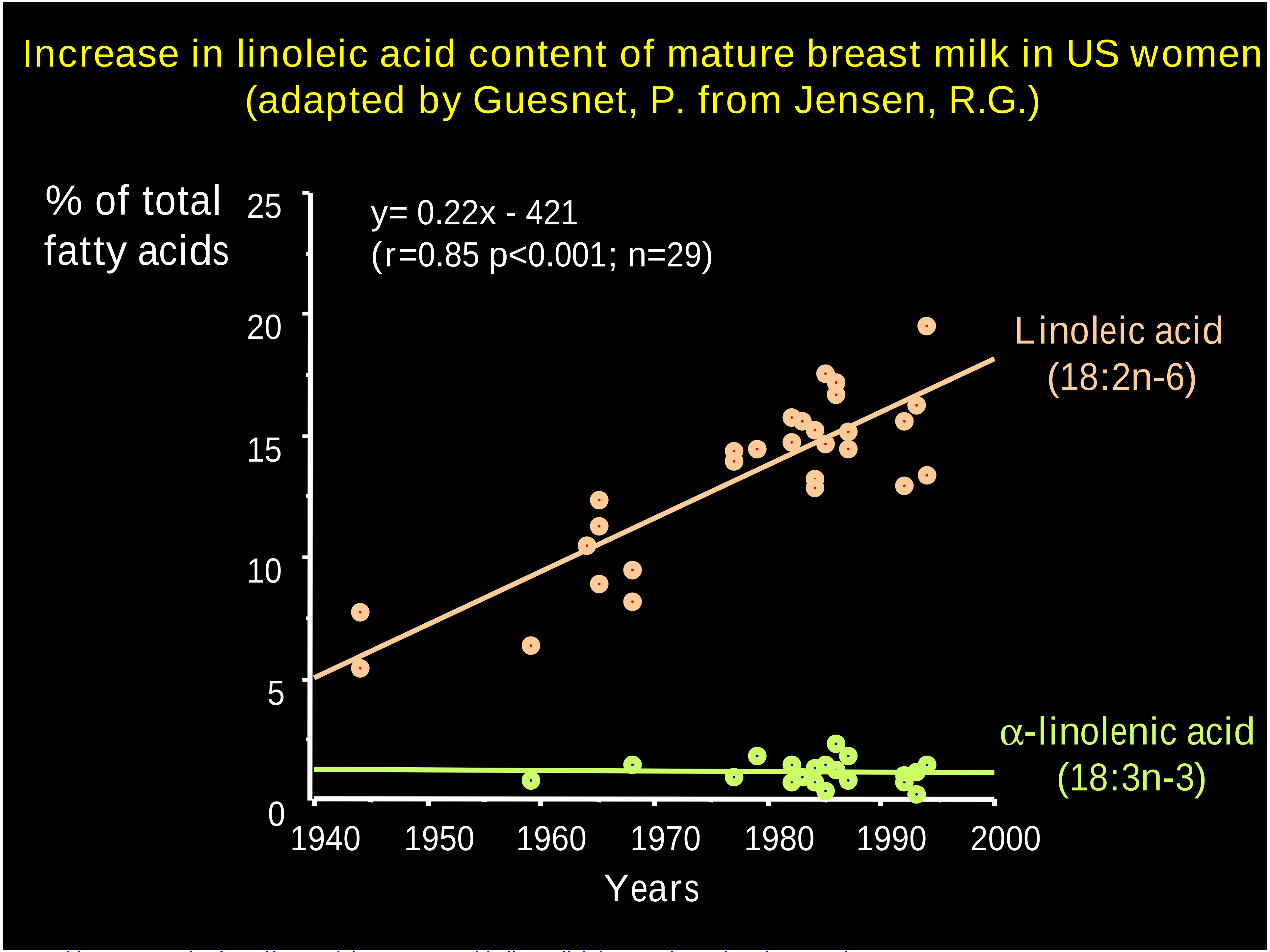
- Decrease in physical activity and nonexercise activity thermogenesis

? • Changes in the qualitative composition of food earlier in life

PERCENTAGE OF CHILDREN 6 TO 11 MONTHS OF AGE ABOVE THE 95th PERCENTILE OF THE WEIGHT-FOR-LENGTH GROWTH REFERENCE,1971 THROUGH 1974 TO 1988 THROUGH 1994

SURVEY	BOYS, % (SE)	GIRLS, % (SE)
All races		
NHANES I	†	†
NHANES II	4.0 (1.3)	6.2 (2.4)
NHANES III	7.5 (1.1)	10.8 (1.2)
White		
NHANES I	†	†
NHANES II	2.7 (1.3)	6.5 (2.8)
NHANES III	7.3 (1.3)	11.1 (1.4)
Black		
NHANES I		
NHANES II	9.0 (3.3)	‡
NHANES III	9.5 (3.2)	10.7 (2.9)
Mexican-American		
HHANES	4.5 (2.7)	7.3 (3.1)
NHANES III	12.2 (4.4)	16.3 (3.9)

- National Health and Nutrition Examination Survey (NHANES) I, 1971 through 1974
- NHANES II, 1976 through 1980
- Hispanic Health and Nutrition Examination Survey (HHANES), 1982 through 1984
- NHANES III, 1988 through 1994


Increase in linoleic acid content of mature breast milk in US women
(adapted by Guesnet, P. from Jensen, R.G.)
% of total fatty acids
y= 0.22x - 421
(r=0.85 p<0.001; n=29)
Linoleic acid (18:2n-6)
α-linolenic acid (18:3n-3)
0
5
10
15
20
25
1940
1950
1960
1970
1980
1990
2000
Years

Milk fatty acid composition is a reflection of dietary lipids in breast-feeding baboons

(Sarkadi-Nagy et al, 2004)

		Female's feed	Breast milk
?•SFA		30.4 ± 0.7	27.9 ± 8.5
?ÔMUFA		35.3 ± 1.0	38.9 ± 8.4
PUFA			
n-6	Linoleic acid (LO)	27.9 ± 1.4	27.2 ± 4.0
	Arachidonic acid	0.24 ± 0.04	0.62 ± 0.12
n-3	α-linolenic acid (LL)	2.58 ± 0.22	2.12 ± 0.53
	EPA	0.85 ± 0.11	0.34 ± 0.13
	DHA	0.73 ± 0.03	0.68 ± 0.22
	LO/LL	10.8	12.8

Fatty acid intake in US women on the basis of two food-frequency questionnaires and 2 wk of diet records and the fatty acid composition of adipose tissue[1] (Garland et al, 1998)

Fatty acid	Questionnaire 1 Amount	Questionnaire 1 Proportion	Questionnaire 2 Amount	Questionnaire 2 Proportion	Diet records[2] Amount	Diet records[2] Proportion	Adipose tissue composition
	g/d %	*of total fatty acids*	*g/d*	*% of total fatty acids*	*g/d*	*% of total fatty acids*	*% of total fatty acids*[3]
Saturated	23.9 ± 8.4	39.2 ± 5.1	22.4 ± 8.3	38.7 ± 4.6	22.7 ± 6.7	38.8 ± 4.1	21.6 ± 6.0
Polyunsaturated	13.0 ± 5.6	21.1 ± 4.7	12.4 ± 4.8	21.4 ± 3.9	13.0 ± 4.5	22.1 ± 4.1	21.7 ± 3.9
Monounsaturated	24.5 ± 9.0	39.7 ± 2.7	23.2 ± 8.3	39.9 ± 3.0	23.0 ± 6.7	39.1 ± 2.4	56.0 ± 4.3
Palmitic	12.7 ± 4.4	20.7 ± 2.1	11.7 ± 4.0	20.4 ± 2.1	NA	NA	15.3 ± 5.3
Linoleic	11.1 ± 5.0	18.1 ± 4.3	10.8 ± 4.4	18.5 ± 3.6	NA	NA	18.5 ± 3.5
Linolenic[4]	1.2 ± 0.5	2.0 ± 0.5	1.1 ± 0.4	1.9 ± 0.5	NA	NA	0.9 ± 0.2
Arachidonic	0.1 ± 0.05	0.2 ± 0.08	0.1 ± 0.04	0.2 ± 0.07	NA	NA	0.7 ± 0.4
Oleic	22.3 ± 8.4	36.2 ± 2.8	21.4 ± 7.8	36.7 ± 3.2	NA	NA	40.5 ± 2.9
Total *trans*	2.8 ± 1.3	4.7 ± 1.4	2.8 ± 1.4	4.8 ± 1.5	NA	NA	6.1 ± 1.3
trans 18:1	2.2 ± 1.1	3.7 ± 1.3	2.3 ± 1.2	3.8 ± 1.4	NA	NA	3.9 ± 1.1
trans 18:2	0.4 ± 0.2	0.7 ± 0.2	04 ± 0 2	0.7 ± 0.2	NA	NA	0.9 ± 0.2

1 x– ± SD; *n* = 140. NA, not available. The second food-frequency questionnaire was completed 18 mo after the first. The second 1 wk diet record was
collected 6 mo after the first. The adipose tissue aspirate was collected at the time of the completion of the second diet record.

2 Information on specific fatty acids was not available from the ESHA database (23) used for analysis.

3 % by weight of methyl esters.

4 Includes all isomers of 18:3.

MAJOR FATTY ACID COMPOSITION OF INFANT FORMULAS AND BREAST MILK (Guesnet *et al.*, 1999)

FATTY ACID	INFANT FORMULAS DHA-supplemented High in EPA	INFANT FORMULAS DHA-supplemented Low in EPA	BREAST MILK*
	% by wt	% by wt	% by wt
Saturated	46.4	46.4	47.5 ± 2.1
Monounsaturated	33.8	34.0	36.7 ± 2.5
18:2n-6 Linoleic	17.8	17.7	11.8 ± 3.3
20:4n-6 ARA	0.05	0.05	0.24 ± 0.09
18:3n-3 α-Linolenic	~~0.85~~	~~1.10~~	~~0.55 ± 0.25~~
20:5n-3 EPA	0.35	0.10	0.03 ± 0.02
22:6n-3 DHA	0.45	0.45	0.14 ± 0.05

* x ± SD of breast milk collected on day 42 of lactation (n = 15)

NUTRITIONAL INTAKES IN AMERICAN AND FRENCH INFANTS (Courtesy of Dr M.F. Rolland-Cachera)

		AMERICAN*	FRENCH * *	FRENCH * * *
YEARS OF COLLECTION		1988-1991	1986-1987	1997
AGE (Months)		12-24	10-24	13-18
ENERGY INTAKE (kcal)		1289	1184	1040
NUTRIENTS (%)	Proteins	15	16	17
	Carbohydrates	53	54	51
	Lipids	34	30	31
	Saturated	14	14	n.d.
	Monounsaturated	12	10	n.d.
	Polyunsaturated	*5*	*3*	*n.d.*

* NHANES III (phase1), 1994

* * Deheeger *et al.*,1994 (same infants at 10 and 24 months)

*** Boggio *et al.*, 1999

SURPOIDS et OBESITE de l'ENFANT

(Ailhaud & Guesnet- Obesity Reviews- Février 2004)

?á Au cours des dernières décennies, des changements notables mais passés inaperçus sont intervenus dans la composition en acides gras des lipides ingérés par les futures mères et par les nouveaux-nés

?: Si l'on considère la prévention comme essentielle, une plus grande attention devrait être portée sur des aspects à la fois quantitatifs et QUALITATIFS portant sur la nature des lipides alimentaires.

Conclusions

Efficient use of $\omega 3$ polyunsaturated fatty acids requires the *simultaneous reduction* of $\omega 6$ polyunsaturated fatty acids in the content of formula milk and food products, and their substitution with saturated/monounsaturated fatty acids

NICE / *GENEVA*

Ez-Zoubir AMRI

Jérome AUBERT (*former*)

Nathalie BELMONTE (*former*)

Sophie DESSOLIN (*former*)

Blaine PHILLIPS (*former*)

Christian DANI

Florence MASSIERA

Raymond NEGREL

Perla SAINT-MARC

Josiane SEYDOUX

JOUY-en-JOSAS / *KYOTO*

Philippe GUESNET

Takuya KOBAYASHI

Takiko MURATA

Shuh NARUMIYA

- Pregnancy weight gain has increased from 1960 to 2000 in Finland (?Ý1.1 kg)

- Higher pregnancy weight gain is associated with higher mean child's birthweight and a higher proportion of high birthweight babies in all cohorts

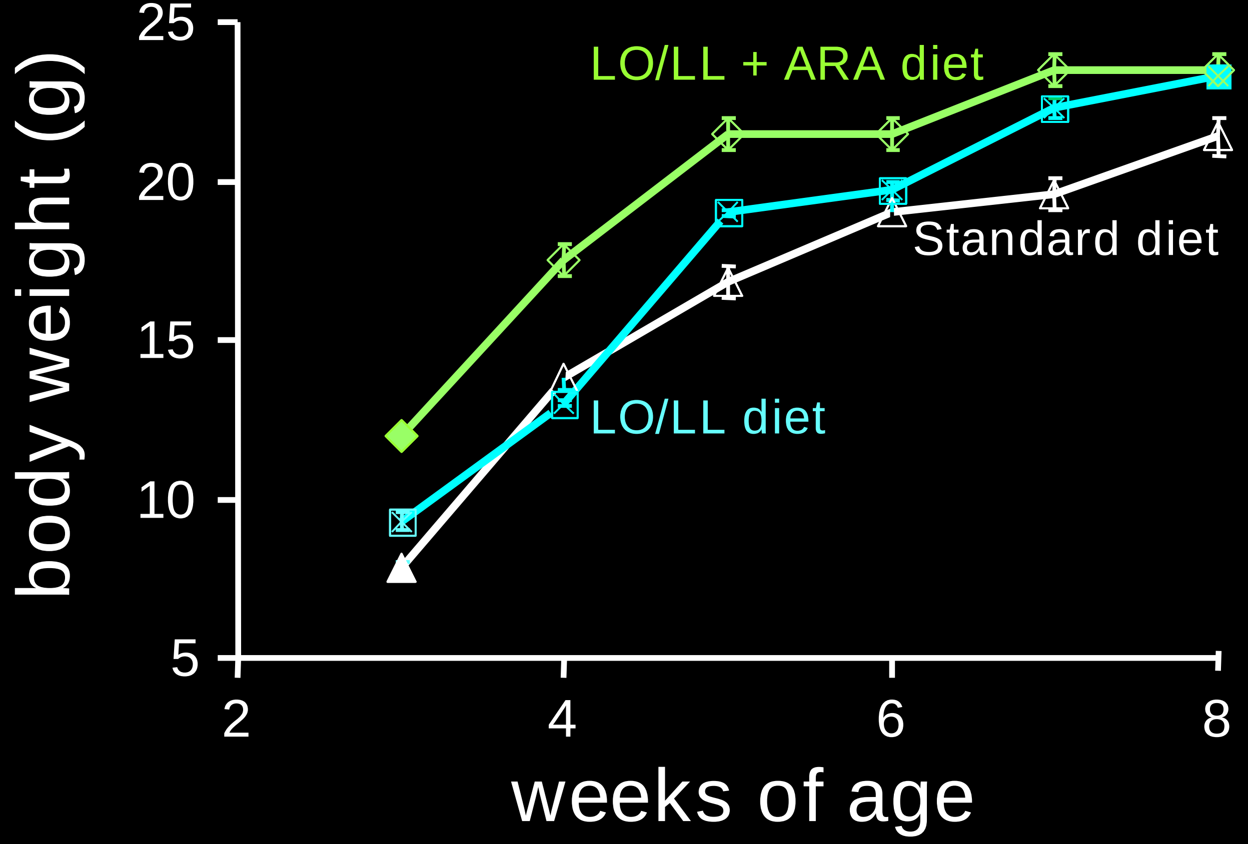
(Kinnunen *et al*, Int. J. Obes. 2003, 1-6)

Relationships between polyunsaturated fatty acids and prostaglandin production

- In adult humans, α-linolenic acid intake decreases severely prostaglandin synthesis but not the conversion of linoleic acid to arachidonic acid (Adam et al, 1986). *However*, in normal term enfants receiving 16 % linoleic acid and from 0.4 to 3.2 % α-linolenic acid (LO/LL ratios from 44 to 5), lower arachidonic acid and higher DHA levels were observed and, interestingly, associated with lower body weight (Jensen et al, 1997).

- In mice, increasing total fat (5-20 % fat) and decreasing $\omega 6/\omega 3$ ratios (0.1 up to >100) lead to a dramatic decrease of *prostacyclin* production (Broughton et Waide, 2002).

Dietary arachidonic acid abrogates the anti-adipogenic effect on body weight of α–linolenic acid-enriched diet



ABBOTT LABORATORIES' ROSS PRODUCTS DIVISION LAUNCHES PRETERM INFANT FORMULAS SUPPLEMENTED WITH DHA AND ARA

For term infants, the Ross Products Division recently introduced Similac® Advance® with Iron, an infant formula that contains DHA and ARA, for those parents and health care professionals who want to feed a term infant formula supplemented with these fatty acids. Similac Advance has been found to support visual and cognitive development like that of the breastfed infant.