SATURATED FATTY ACIDS
A new paradigm is necessary

Nutrients before all….

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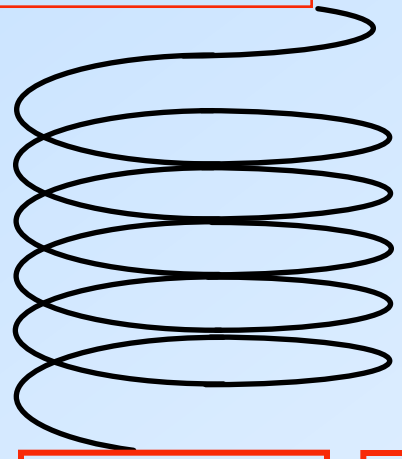
No conflict of interest for this conference

SATURATED FATTY ACIDS

- We eat them but we make «them» (one)
- Metabolism
- Important specific functions
- Problems with CVD and MS biomarkers

Saturated fatty acids
« We do synthesize them» : (human, animals, plants…)

Sugars, starch, alcohol…….



synthesis

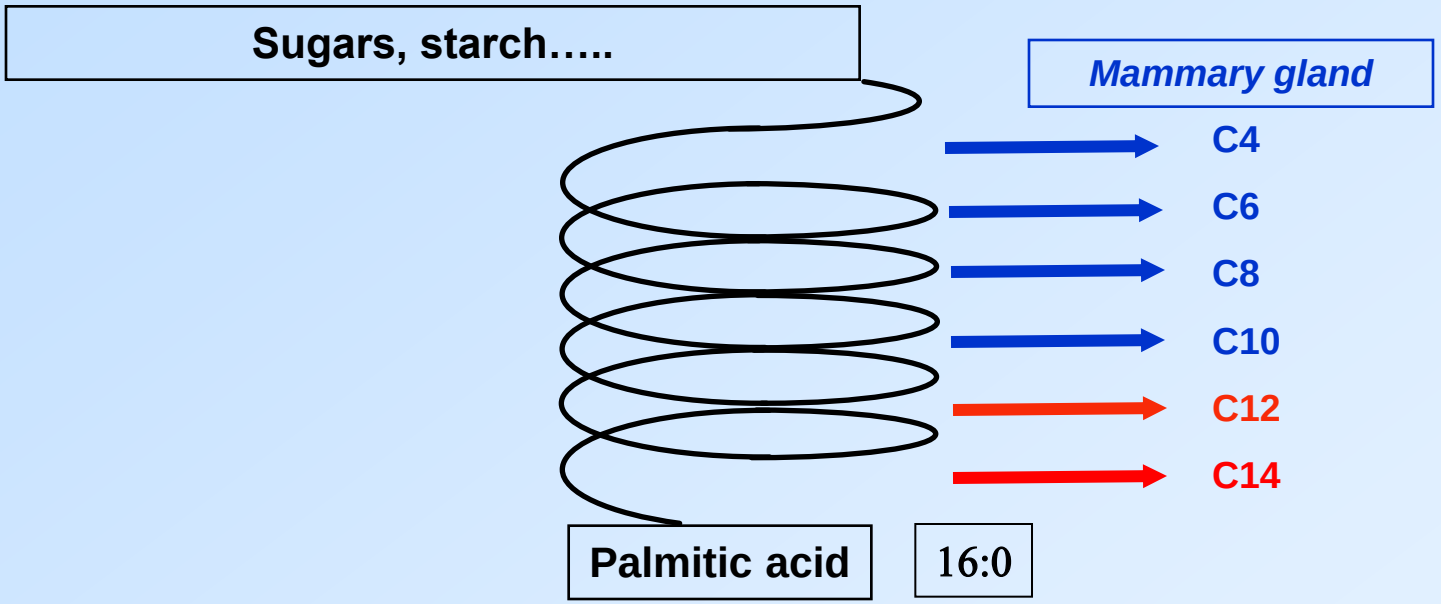
Palmitic acid | 16:0

elongation

Stearic acid | 18:0

Aarsland 2008, Chong 2008, Forsythe 2008, Wilke 2009

In addition,mammary gland synthesizes the short and middle chain saturates (C4-C10), plus lauric (C12) and myristic acid (C14)



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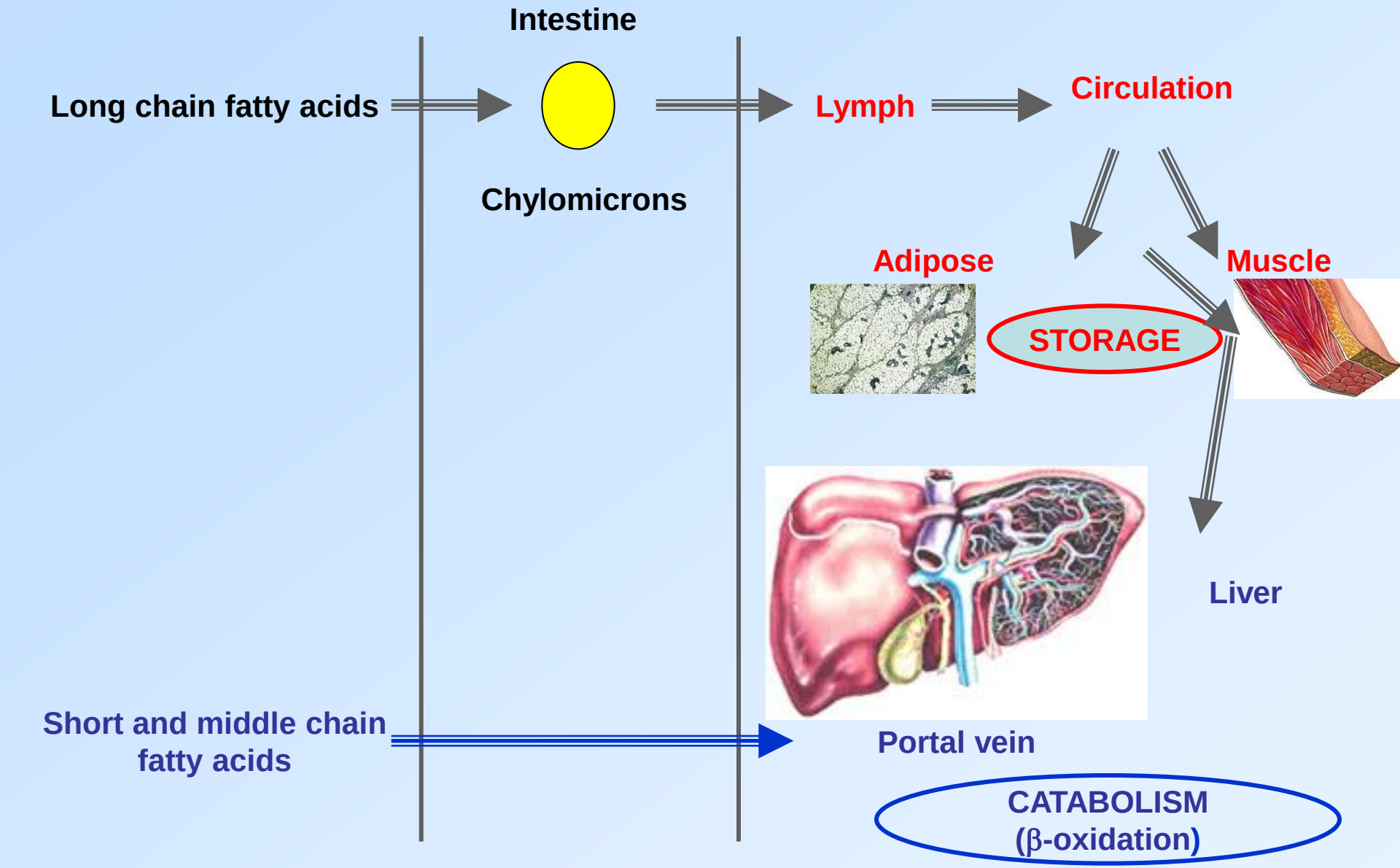
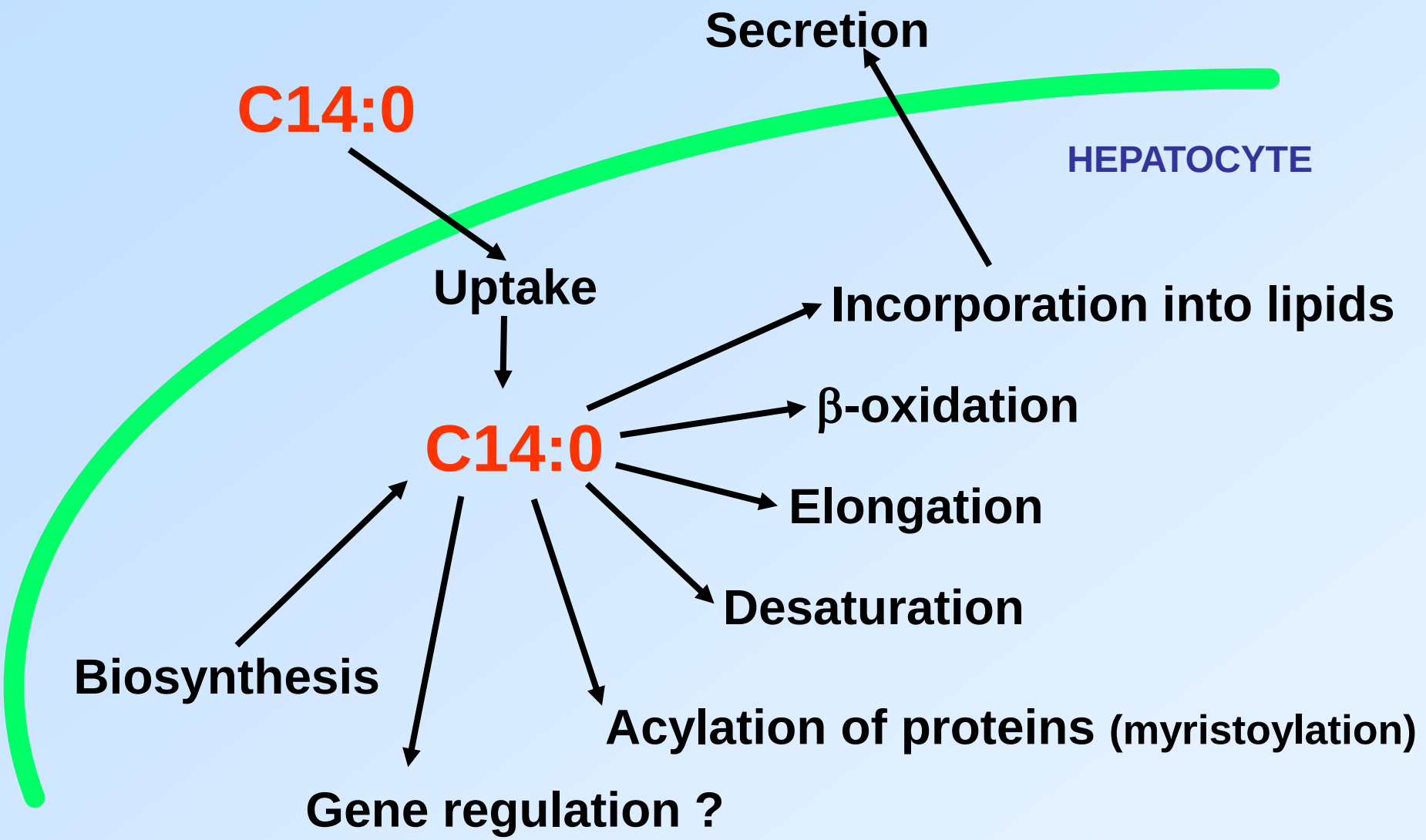
Comparative absorption of saturated fatty acids



Myristic / Palmitic acid metabolism



Rioux et al. (2000) , Rioux et al. (2002), Legrand et al. (2002), Rioux et al. (2003), Jan et al. (2004), Rioux et al. (2005), Rioux et al. (2006), Rioux et al. (2007), Rioux et al. (2008),

METABOLIC DIFFERENCES

- **Short and middle chain SFA have a specific and « safe » metabolism,**
- **Myristic acid and palmitic acid have not the same metabolic fate in the cell :**
- **Myristic acid is rapidly β-oxidized, weakly secreted in the form of TG-VLDL, but strongly elongated into palmitic acid. No accumulation !**
- **Palmitic acid is stored and secreted in the form of TG, weakly elongated into stearic acid. Also main product of *de novo* lipogenesis, it accumulates in the cell ! *« Sugaric acid ? »***
- **Stearic acid is less synthesized (than palmitic), actively desaturated into oleic acid. No accumulation ! « *Pre-Oleic acid ? »***

Rioux et al. (2000) , Rioux et al. (2002), Legrand et al. (2002), Rioux et al. (2003), Jan et al. (2004), Rioux et al. (2005), Rioux et al. (2006), Rioux et al. (2007), Rioux et al. (2008), Beauchamps et al., 2009

SATURATED FATTY ACIDS

- We eat them but we make them

- Metabolism

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- Problems with CVD and MS biomarkers

Saturated fatty acids functions at a glance

(in addition to energetical function)

C4 butyric

- **fuel for intestinal mucosa and microbiota**
- **Immunostimulation**
- **Cellular differentiation and inhibition of tumor proliferation *in vivo* and *in vitro* (Induction of apoptosis)**

C6 caproïc

C8 caprylic

C10 capric

C12 lauric

C14 myristic

C16 palmitic

C18 stearic

C20 arachidic

C22 behenic

C24 lignoceric

Saturated fatty acids functions at a glance

(in addition to energetical function)

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C20 arachidic

C22 behenic

C24 lignoceric

- **Less fat deposition**
- **C8 ↓ VLDL secretion (inhibition of apo B synthesis)**
- **Hypocholesterolemic effect (C8, C10)**
- **Ghrelin acylation (C8)**
- **Antifungal and antiviral properties**

Saturated fatty acids functions at a glance

(in addition to energetical function)

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C16 palmitic

C18 stearic

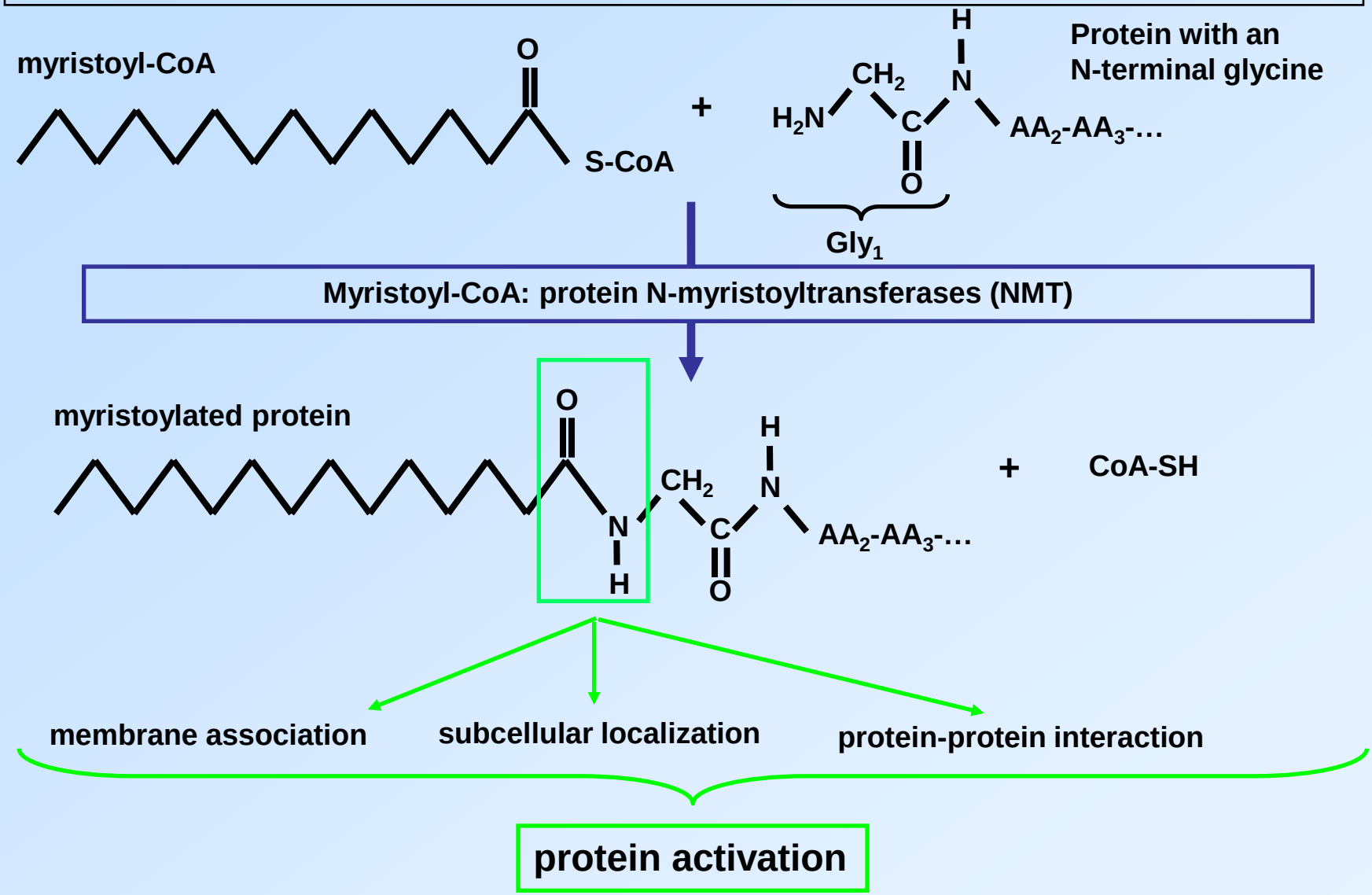
C20 arachidic

C22 behenic

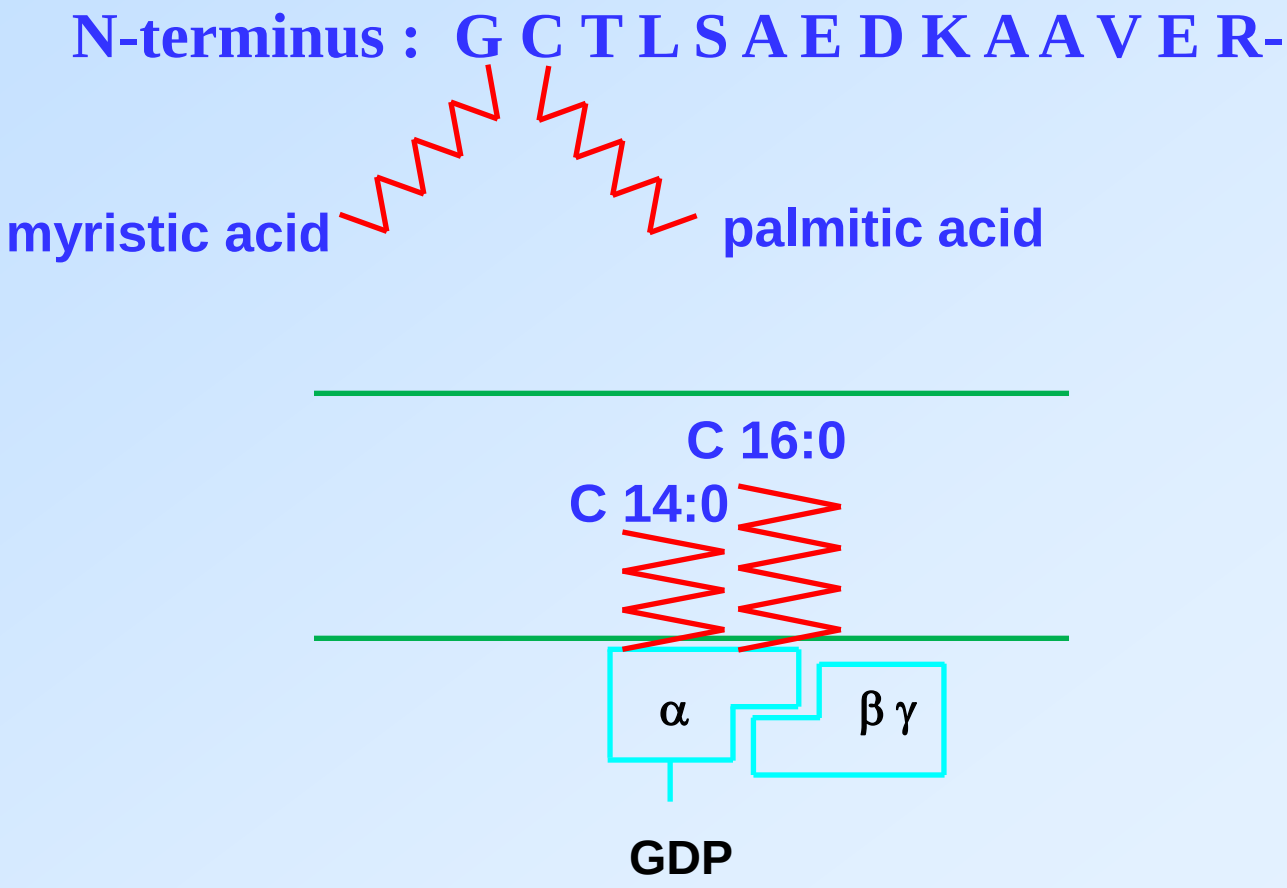
C24 lignoceric

- **Specific acylation of proteins**
- **Activation of conversion from C18:3 n-3 towards EPA + DHA**
- **Activation of sphingolipids synthesis**

N-terminal myristoylation



Myristoylation and palmitoylation of the α-subunit of heterotrimeric G proteins



Wedegaertner, 1998

Saturated fatty acids functions at a glance

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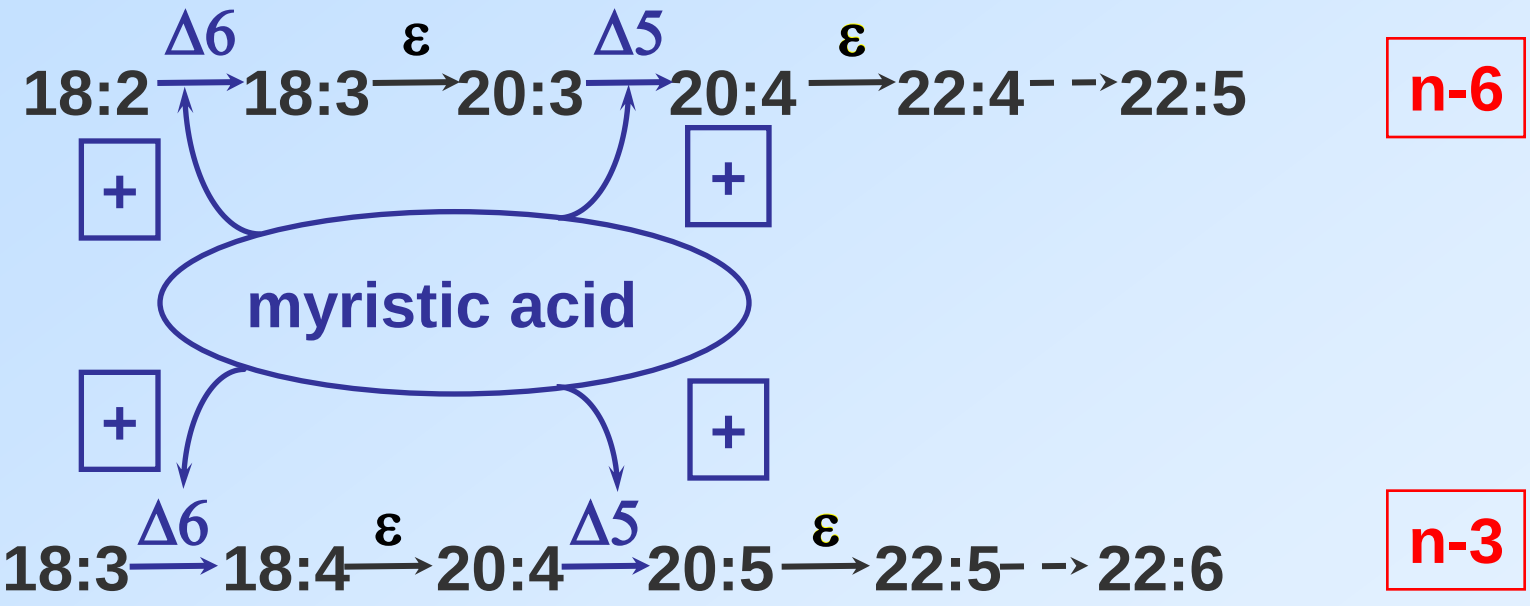
- Specific acylation of proteins
- **Activation of conversion from C18:3 n-3 towards EPA + DHA**
- Activation of sphingolipids synthesis

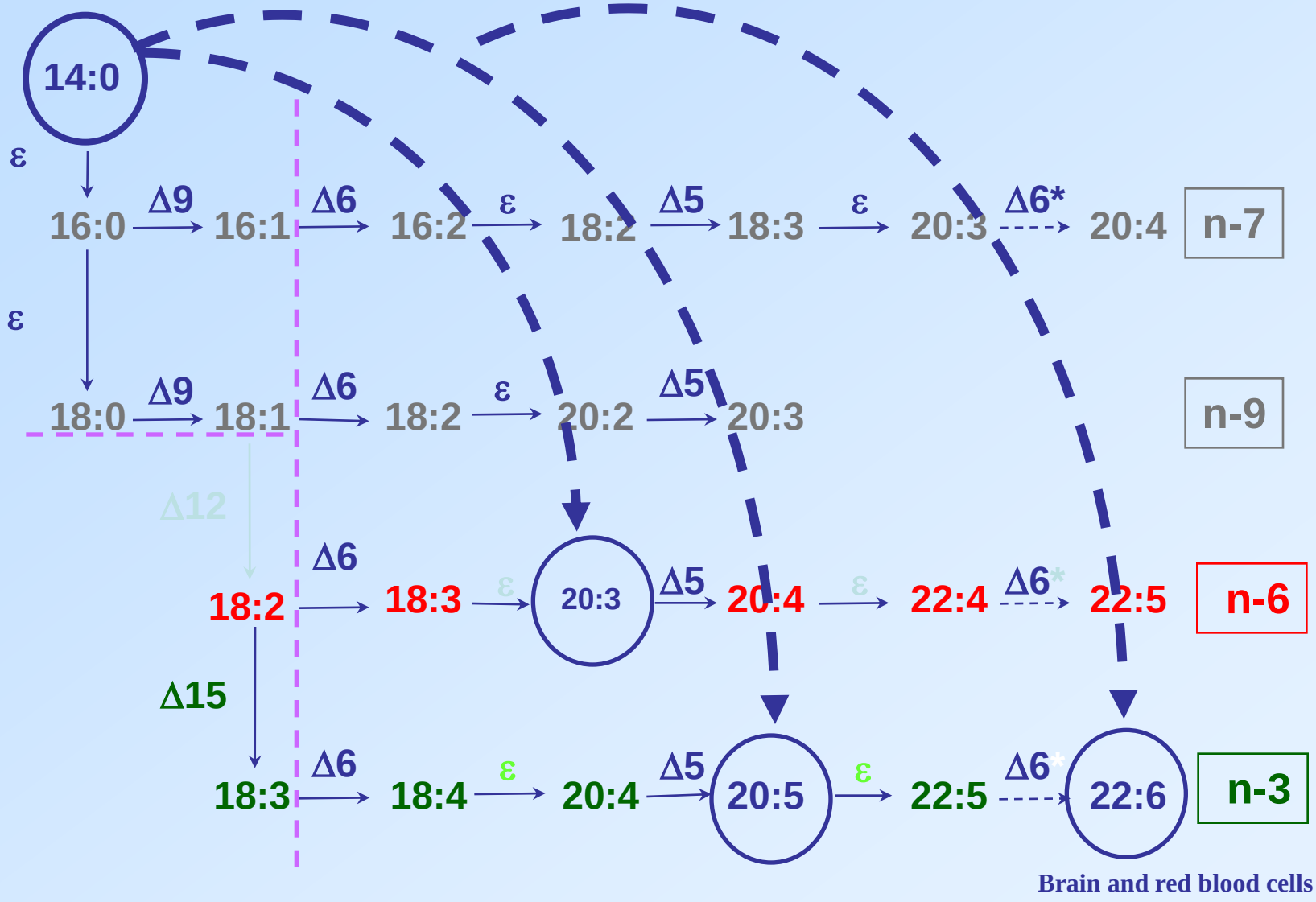
Role of myristic acid on PUFA metabolism (in vitro)



NADH-cyt b5 reductase, component of desaturase complex is myristoylated

Jan et al., 2004; Beauchamp et al., 2007

Effect of myristic acid on PUFAs composition in the rat *in vivo* and in human



Rioux et al., 2005, Dabadie et al., 2005, Rioux et al., 2008

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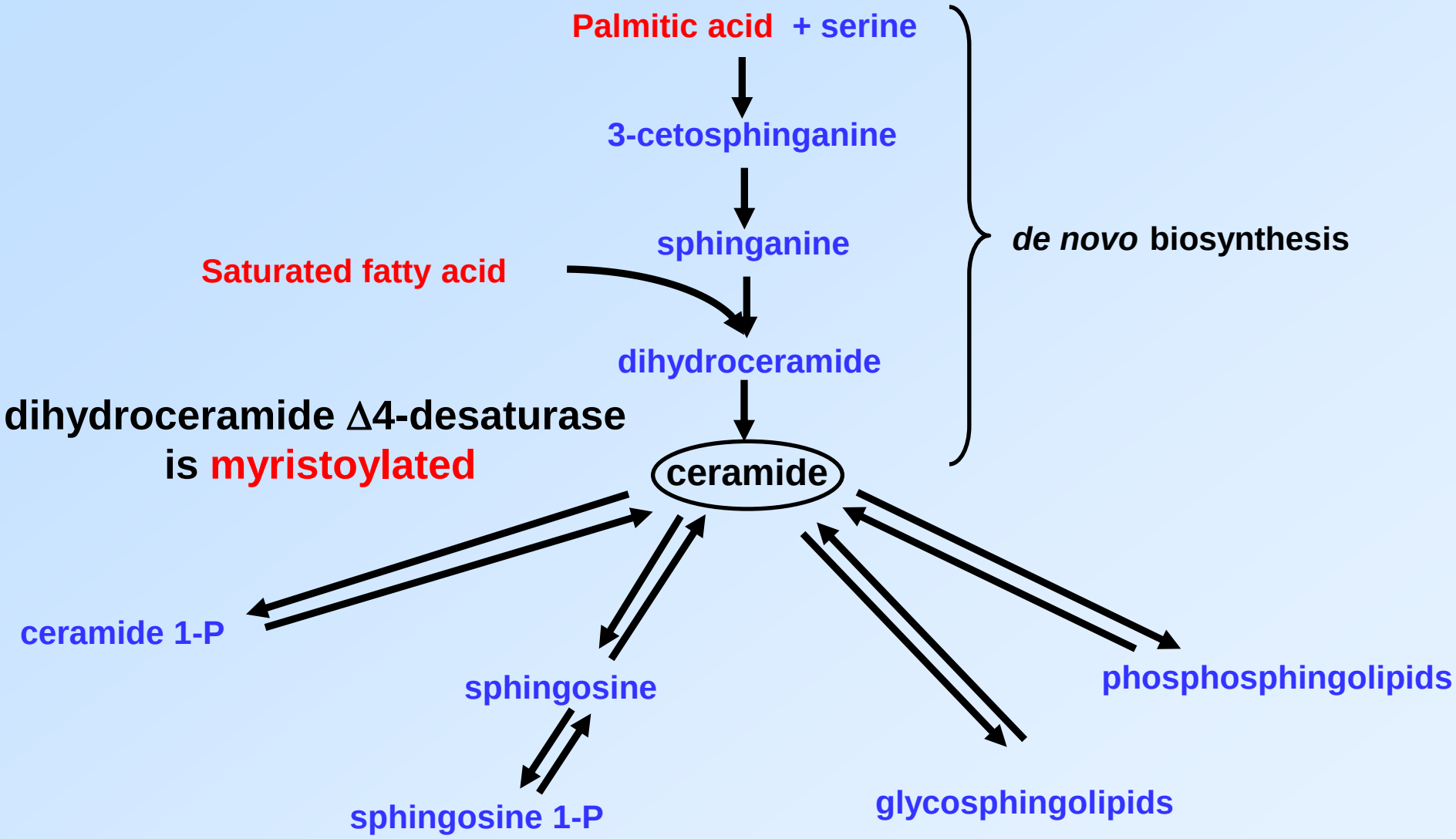
- Specific acylation of proteins
- Activation of conversion from C18:3 n-3 towards EPA + DHA
- **Activation of sphingolipids synthesis**

Importance of SFA for sphingolipids biosynthesis in animals



Beauchamp et al., 2007

Saturated fatty acids functions at a glance

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- **Componant of sphingolipids and phosphoglycerids**
- **Acylation of some proteins (cell adhesion molecules, receptors, channels……..)**
- **Lung surfactant (Dipalmitoyl PC)**
- **Precursor of PEA (palmitoylethanolamide, neuro protective and neuroanti inflammatory effects)**

Saturated fatty acids functions at a glance

(in addition to energetical function)

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C24 lignoceric

- stearoylation of proteins (transferrine receptor

- Active desaturation to oleic acid

- componant of phospholipids

Saturated fatty acids functions at a glance

(in addition to energetical function)

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C8 caprylic

C10 capric

C12 lauric

C14 myristic

C16 palmitic

C18 stearic

C20 arachidic

C22 behenic

C24 lignoceric

1 / 3 of phospholipids fatty acids : structural role

Saturated fatty acids functions at a glance

(in addition to energetical function)

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C6 caproïc

C8 caprylic

C10 capric

C12 lauric

C14 myristic

C16 palmitic

C18 stearic

C20 arachidic

C22 behenic

C24 lignoceric

- Nervous structure (myelinisation)

Saturated fatty acids functions at a glance

(in addition to energetical function)

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C24 lignoceric

SO WHAT ?

Nutrients with important functions

SATURATED FATTY ACIDS

- We eat them but we make them

- Metabolism

- Important specific functions

- Problems with CVD and MS biomarkers

RCT with hard endpoints :

Even the most positive (Hooper et al, 2015) : NS on total mortality, CVD mortality, myocardial infraction, non-fatal myocardial infraction, stroke, coronary heart disease events and coronary heart disease mortality (only the composite « combined cvd events »)

RCT with surrogate endpoints :

Mensink et al, 2016 : effect of reduction/replacement on LDL, total, total/HDL…., but no evidence of beneficial effects ? Translation from markers to CVD endpoints ? And SFA/ PUFA without any distinction is not sufficient anymore (omega6)

Observational studies (meta-analysis, cohorts)

Association between SFA and CVD risk :

⊕	⊖	Neutral
Garcia 1980	Gillman 1997	Shekelle 1981
Mc Gee 1984	He 2003	Kushi 1985
Esrey 1996	Mozzafarian 2004	Posner 1991
Boniface 2002	Jakobsen 2009	Ascherio 1996
Jakobsen 2004	Yamagashi 2009	Pietinen 1997
Xu 2006	Jakobsen 2010 (MI)	Tucke 2005
		Leosdottir 2007

- Meta-analysis (Siri-Tarino 2010) : 21 cohorts

”Overall, despite the conventional wisdom that reduced dietary saturated fat intake is beneficial for CVD health, there is no significant evidence for concluding that dietary saturated fat is associated with an increased risk of CHD or CVD”

- Other meta-analysis: O’Sullivan, 2013; Chowdhury, 2014; Harcomb, 2015, De Souza 2015

➡ ***same results***

- In CAD patients: Puaschitz et al., 2015 ***No association either***

Global risk for SFA

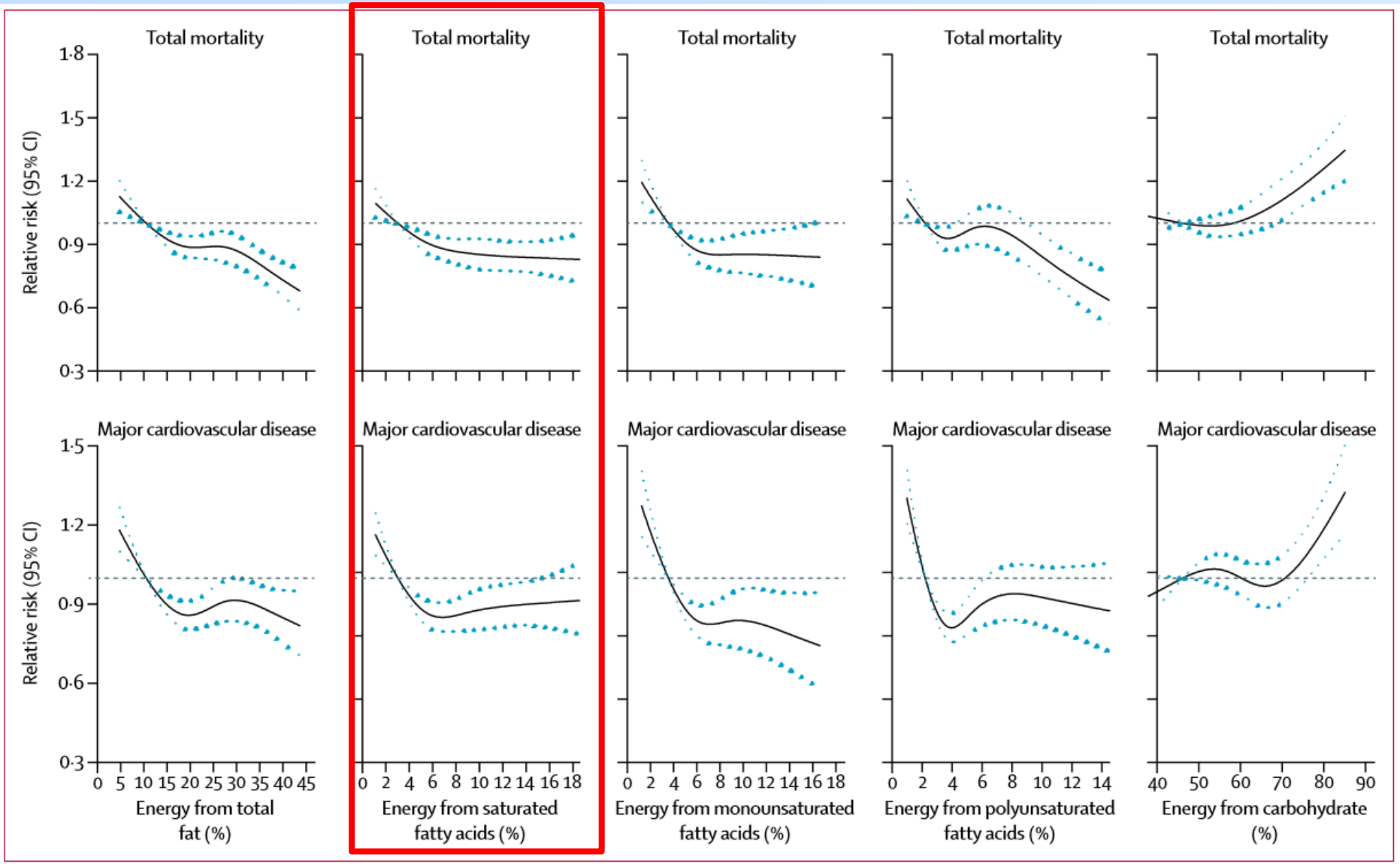


Figure 1: **Association between estimated percentage energy from nutrients and total mortality and major cardiovascular disease (n=135 335)**
Adjusted for age, sex, education, waist-to-hip ratio, smoking, physical activity, diabetes, urban or rural location, centre, geographical regions, and energy intake. Major cardiovascular disease=fatal cardiovascular disease+myocardial infarction+stroke+heart failure.

Saturated fatty acids

General Problems ?

C4 butyric

C6 caproïc

C8 caprylic

C10 capric

C12 lauric

C14 myristic

C16 palmitic

C18 stearic

C20 arachidic

C22 behenic

C24 lignoceric

No problem with the CVD risk ! *Praagman 2016, Mensink 2003…*

Problem with the CVD risk :
Deleterious effects …. in case of excess

Accumulation of palmitic acid : endogenous + exogenous origins

No problem with the CVD risk !

CONCLUSION – SUMMARY

- **No reason for considering SFA "en bloc" anymore, in term of structure and metabolism, in term of functions and in term of deleterious effect as well.**

- **Absence of evidence for specific deleterious effects, need of more precise epidemiological studies (different saturated fatty acids, dose-effects approach, controls…) for the deleterious effects in case of excess**

- **Intervention studies with substitutions for oleic or n-6 polyunsaturated : not beneficial, except substitution for n-3 polyunsaturated**

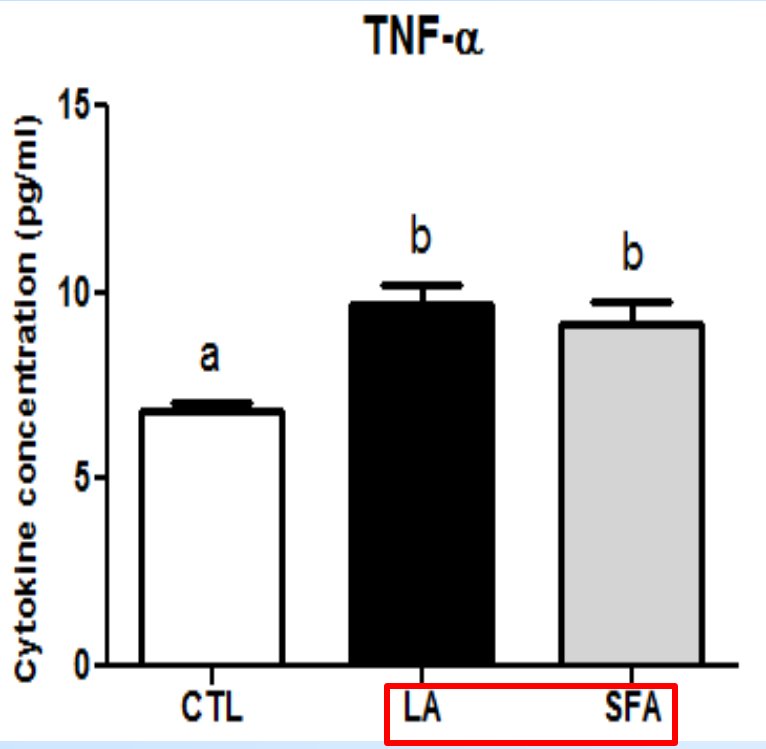
Linoleic acid (C18:2n-6): Physiopathological approach of excess

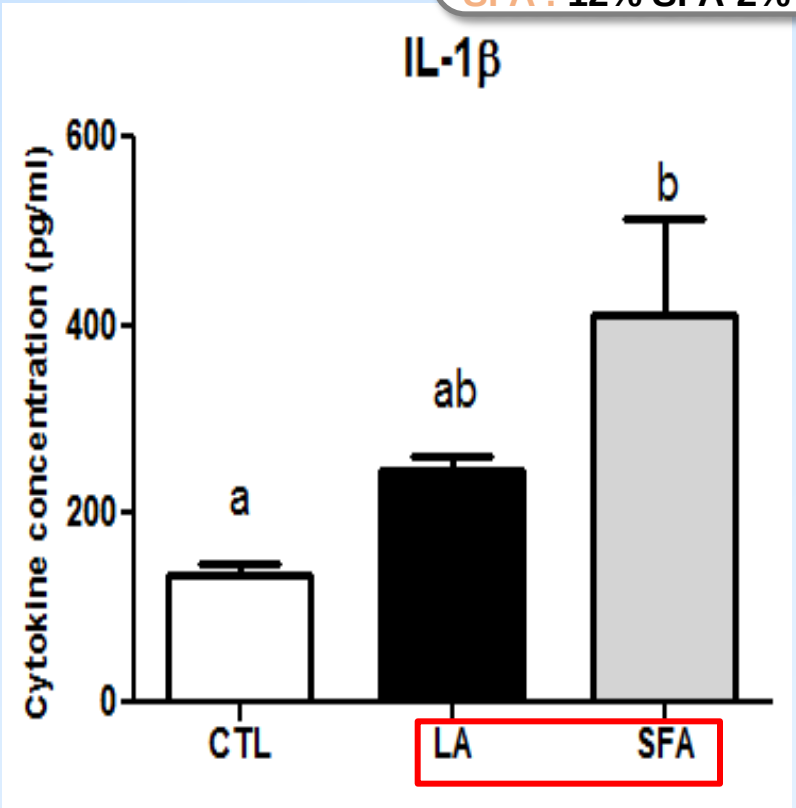
Plasma inflammatory markers

CTL : 12% MUFA-2%LA

LA : 7% MUFA-7%LA

SFA : 12% SFA-2% LA





LA enrichment leads to increased inflammatory markers

(Marchix et al., 2015, J. Nutr Biochem.)

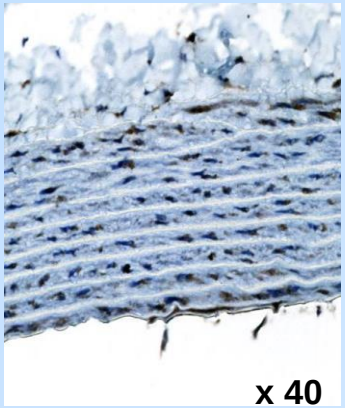
Linoleic acid (C18:2n-6): Physiopathological approach of excess

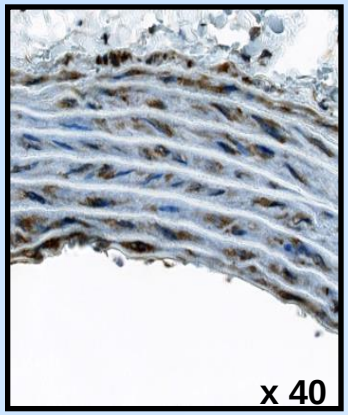
Expression of aortic NF-κB

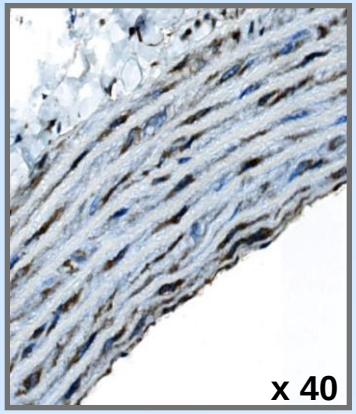
CTL : 12% MUFA-2%LA

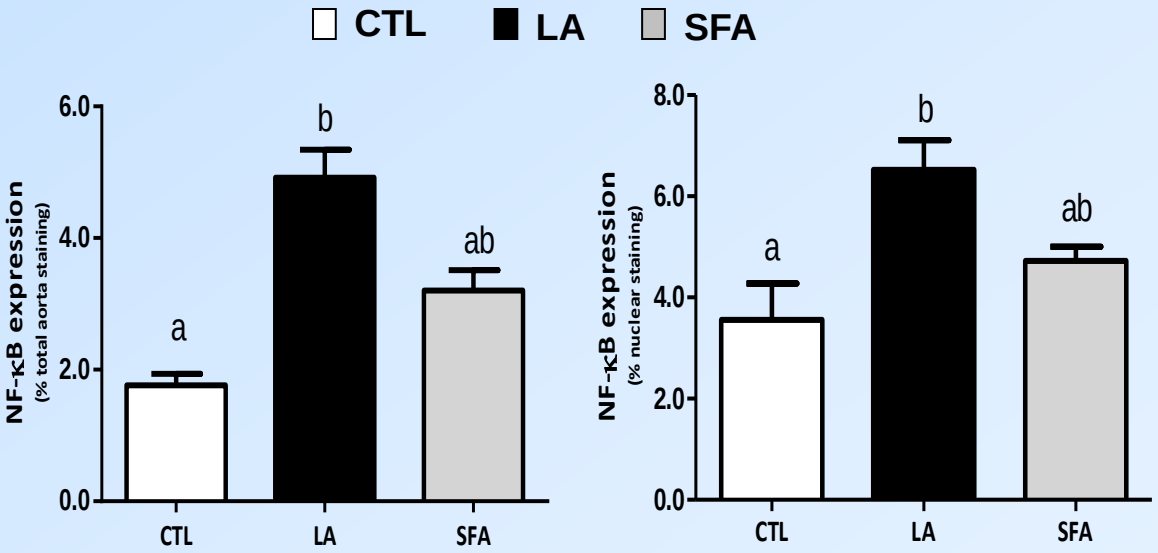
LA : 7% MUFA-7%LA

SFA : 12% SFA-2% LA









NF-κB: nuclear factor –kappa B.

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- Absence of evidence for specific deleterious effects, need of more precise epidemiological studies (different saturated fatty acids, dose-effects approach, controls…) for the deleterious effects in case of excess

- Intervention studies with substitutions for oleic or n-6 polyunsaturated : not beneficial, except substitution for n-3 polyunsaturated

- Intervention studies with substitutions for carbohydrates (sugars starch…) : not beneficial and maybe worse except complex carbohydrates (fibers)

Time for new paradigm and "up to date" recommendations without caricatural old statements of toxicity or eviction……..

New paradigm for SFA guidelines

Let's also speak physiology and nutrition and not only statistics and epidemiology

C4 butyric **+ *fibers, probiotics……***

C6 caproïc

C8 caprylic

C10 capric

C12 lauric

C14 myristic **+ *omega 3***

C18 stearic **(pre-oleic) + oleic acid**

C20 arachidic

C22 behenic

C24 lignoceric

Problem with the CVD risk ?

Only one !…..in case of excess

C16 Palmitic (sugaric ?)

+ Fructose, glucose, alcool….

+ Total energy….

+ Linoleic ?

Need of a balanced and synergic reco for palmitic

…….. So, we tried it in France throw the recommandations of the food safety agency (ANSES)

ANC : NON ESSENTIAL FA : SATURATED FA

For an adult at 2000-2200 kcal/day
Values expressed in % total energy.

		Minimal physiological requirement	RISK PREVENTION					ANC 2010
			Metabolic syndrome, diabetes, obesity	Cardio-vascular diseases	Cancers : breast, colon	Neuro-psychiatric pathologies	Other pathologies : Macular degeneration	
NON ESSENTIAL FA	Lauric acid (C12:0) + myristic acid (C14:0) + palmitic acid (C16:0)	-	-	≤ 8	_	-	-	≤ 8
	Total Saturated FA	-	-	≤ 12	≤ 12	-	-	≤ 12
	Oleic acid C18:1 n-9	-	-	≤ 20	-	-	-	15 - 20
	Others non essential FA	-	-	-	-	-	-	-

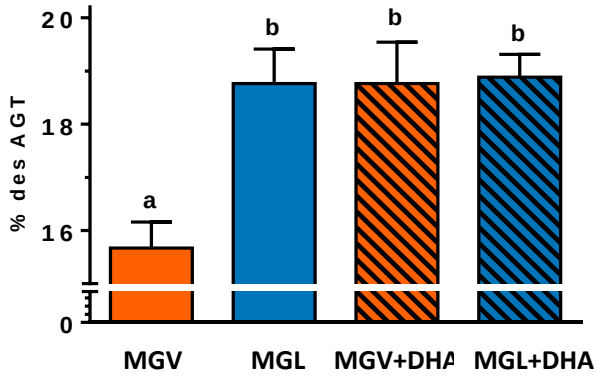
Thanks for your attention

Les lipides laitiers augmentent le statut en DHA des rétines et du cerveau

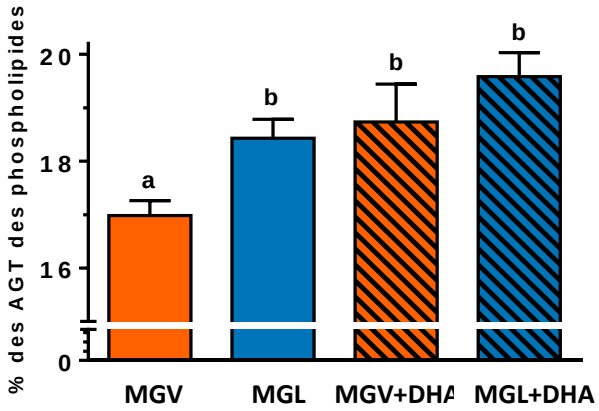
MGV MGL MGV+DHA MGL+DHA

DHA

Rétines



Cerveau



MGL → Acuité visuelle et Neuro-développement

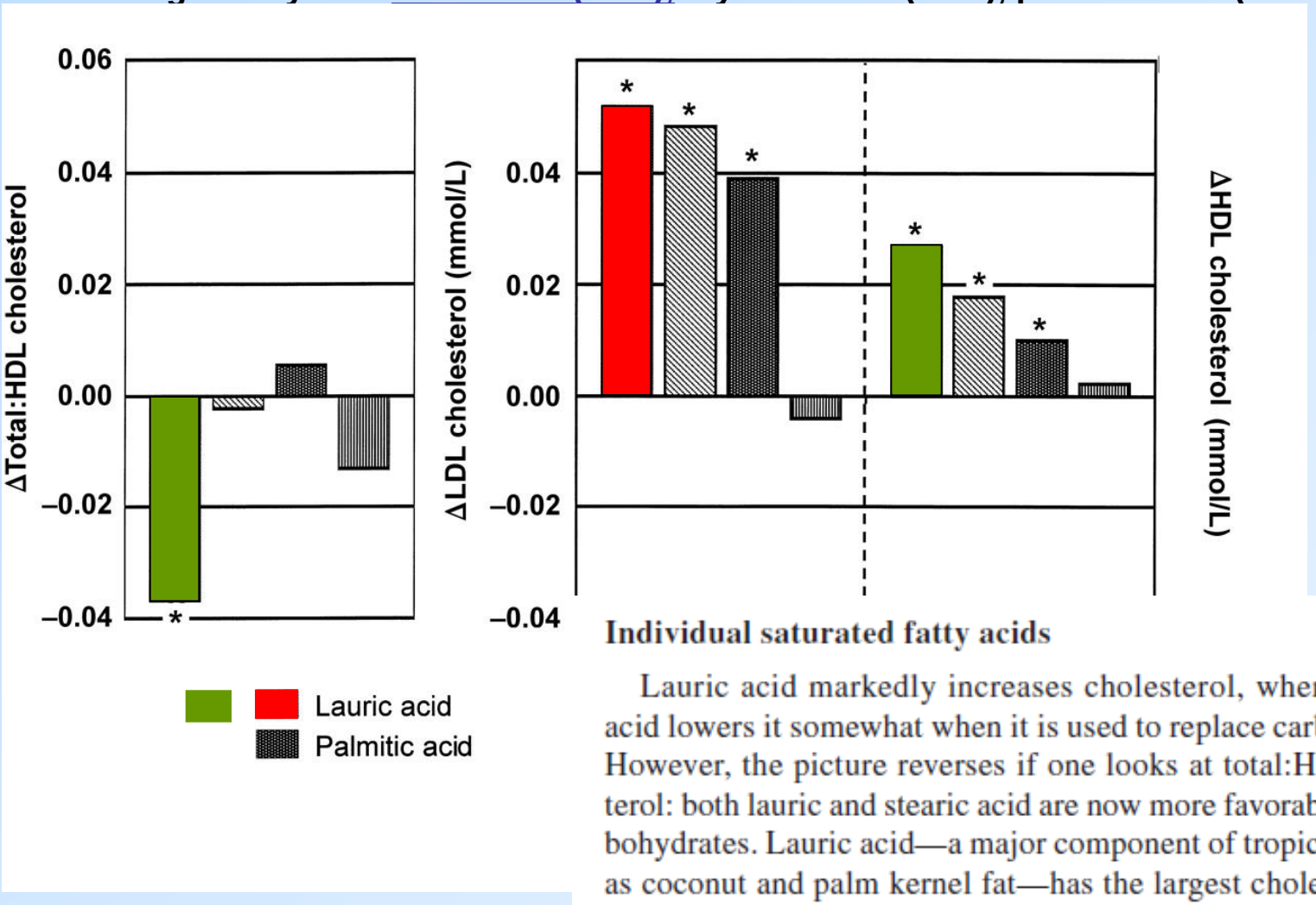
ALA C18:3 —Δ6→ STA C18:4 —ε5→ C20:4 —Δ5→ EPA **C20:5** —ε2-5→ DPA n-3 **C22:5** —ε2→ C24:5 —Δ6→ C24:6 —β-ox→ **DHA C22:6**

Recommendations for lipids and saturated fat

	Year	Lipids	SFA
Canadian Dietary reference intakes (DRI)[1]	2010	20-35% En	As low as possible
Dietary Guidelines for Americans (DGAC/USDA)[2]	2010	20-35% En	< 10% En
AHA/ACC Lifestyle Management Guideline[3]	2013	none	< 7% En
European Food Safety Agency (EFSA)[4]	2010	20-35% En	As low as possible
World Health Organization (WHO)[5]	2008	15-35% En	< 10% En
ANSES, France[6]	2011	35-40% En	**<12% (<8%) En**

[1] http://www.hc-sc.gc.ca/fn-an/nutrition/reference/table/index-eng.php#rvm
[2] http://www.cnpp.usda.gov/DGAs2010-DGACReport.htm
[3] J Am Coll Cardiol 63: 2960-84.
[4] EFSA Journal 8: 1461-1568.
[5] Ann Nutr Metab 55: 56-75.
[6] https://www.anses.fr/sites/default/files/documents/NUT2006sa0359Ra.pdf

Predicted changes (Δ) in the ratio of serum total to HDL cholesterol and in LDL- and HDL-cholesterol concentrations when carbohydrates constituting 1% of energy are replaced isoenergetically with lauric acid (12:0), myristic acid (14:0), palmitic acid (16:0...



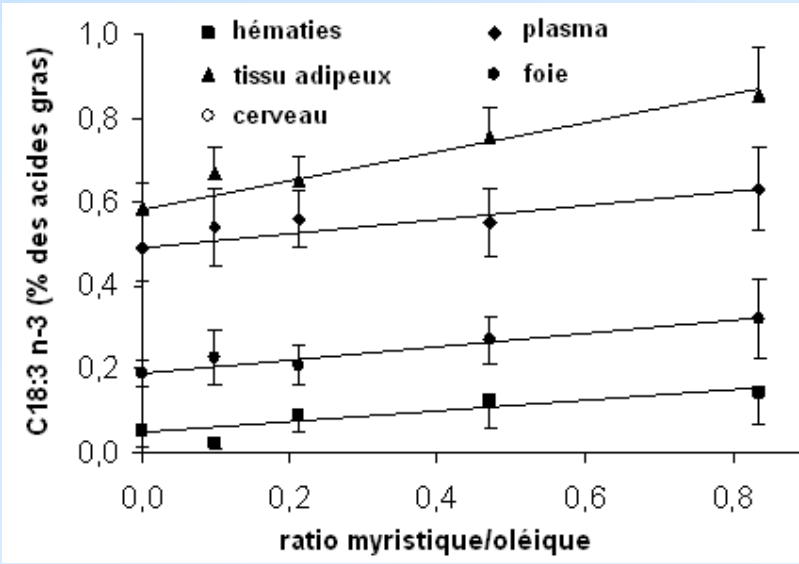
Individual saturated fatty acids

Lauric acid markedly increases cholesterol, whereas stearic acid lowers it somewhat when it is used to replace carbohydrates. However, the picture reverses if one looks at total:HDL cholesterol: both lauric and stearic acid are now more favorable than carbohydrates. Lauric acid—a major component of tropical oils such as coconut and palm kernel fat—has the largest cholesterol-raising effect of all fatty acids, but much of this is due to HDL cholesterol. As a result, lauric acid had a more favorable effect on total:HDL cholesterol than any other fatty acid, either saturated or unsaturated.

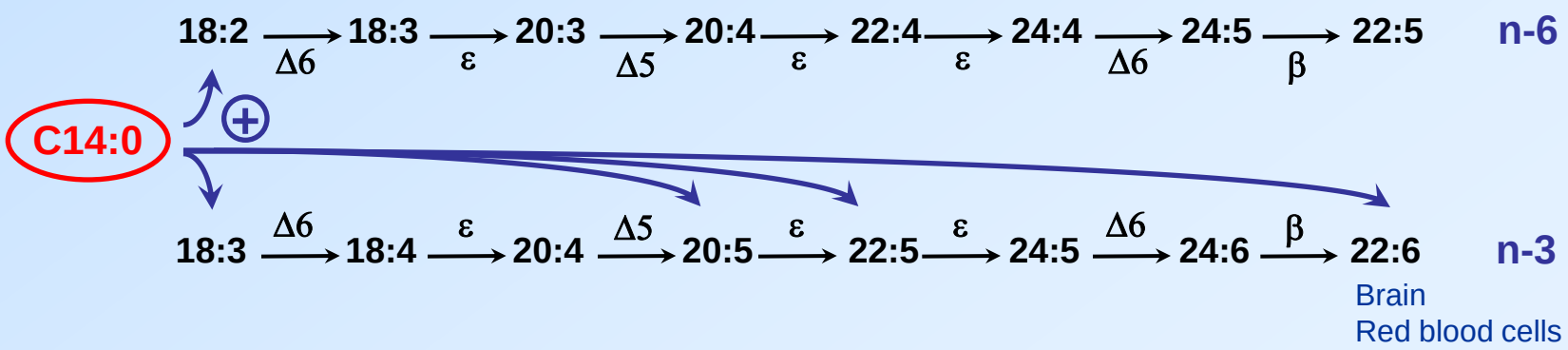
Mensink R P et al. Am J Clin Nutr 2003;77:11

Saturates and PUFAs bioavailability

% AG	MY0	MY5	MY10	MY20	MY30
C14:0	0,02	5,09	9,81	19,41	29,57
C16:0	9,25	14,65	14,83	15,29	15,51
C18:0	3,35	4,87	4,78	3,84	3,01
AG Saturés	13,26	32,69	38,17	45,04	52,52
C 18:1 n-9	76,13	51,94	46,34	41,33	35,47
C 18:2 n-6	6,57	7,04	7,00	7,03	6,91
C 18:3 n-3	1,32	1,38	1,40	1,39	1,38



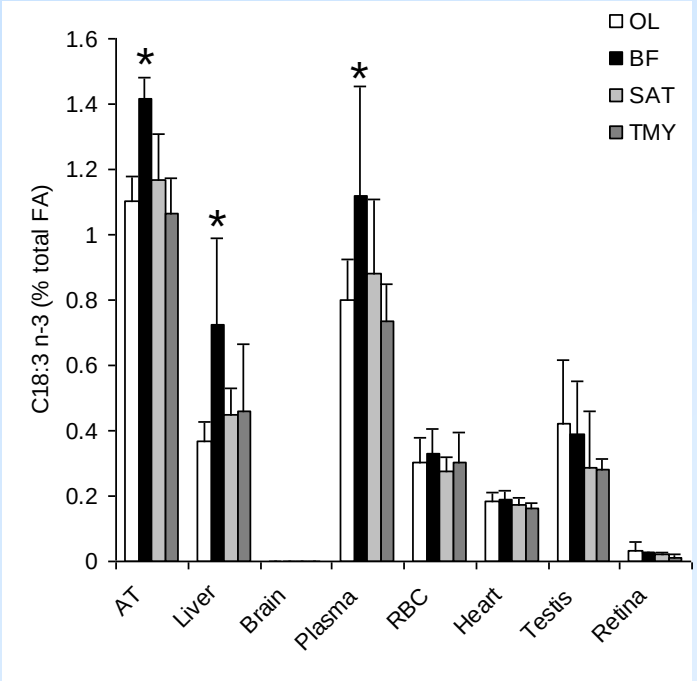
between 2,2% et 6,6% myristic acid (energie) (trimyristin)



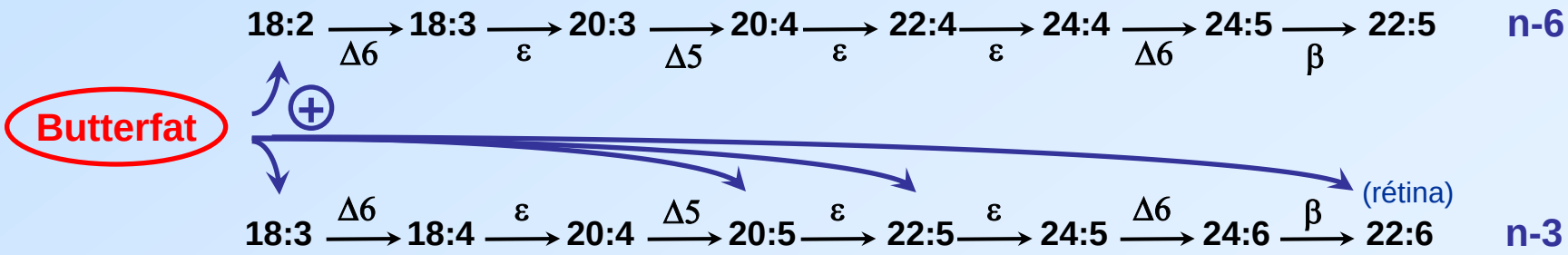
Rioux et al. (2008) Animal 2, 636-644

Saturates and PUFAs bioavailability

% AG	OL	BF	SAT	TMY
C4:0-C10:0		8,93		
C12:0		2,62	2,83	0,11
C14:0	0,02	9,83	9,71	9,75
C16:0	7,83	15,27	16,02	7,51
C18:0	3,06	4,82	2,52	2,68
AG Saturés	11,54	43,83	31,75	20,83
C 18:1 n-9	71,05	33,22	51,28	62,26
C 18:2 n-6	11,82	12,55	11,99	11,69
C 18:3 n-3	2,49	2,61	2,53	2,53



Dairy fat : myristic acid + short and middle chain FA +……..



Legrand et al. (2010) Lipids 45, 975-986

Saturates and PUFAs bioavailability

4 isocaloric and isolipidic diets

	Olive oil	Olive oil + SFAs	Fractionated butter	butter
Olive oil	76.0	48.9		
Canola oil	19.0	28.0	18.0	27.0
Corn oil	5.0	6.4	12.0	11.6
Fractionated butter			66.5	
Butter				61.4
Trilaurin (C12:0		2.0		
Trimyristin (C14:0)		4.9	3.5	
Tripalmitin (C16:0)		8.2		
Tristearin (C18:0)		1.6		

(% lipidic mix)

	Olive oil	Olive oil + SFAs	Fractionated butter	Butter
C4:0			3.6	2.2
C6:0			1.9	1.2
C8:0			1.1	0.7
C10:0			2.4	1.7
C12:0		1.9	2.6	1.9
C14:0		4.9	9.8	6.2
C16:0	7.8	15.0	15.3	18.5
C18:0	3.1	3.8	4.8	6.7
Σ AGS	11.5	26.2	43.8	42.2
C18:1 n-9	71.1	56.5	33.2	33.3
Σ AGMI	74.2	59.4	40.0	39.2
C18:2 n-6	11.8	11.5	12.6	14.9
Σ AGPI n-6	11.8	11.5	13.5	15.2
C18:3 n-3	2.5	2.9	2.6	3.4
Σ AGPI n-3	2.5	2.9	2.7	3.4
C18:2 / C18:3	4.7	4.0	4.8	4.4

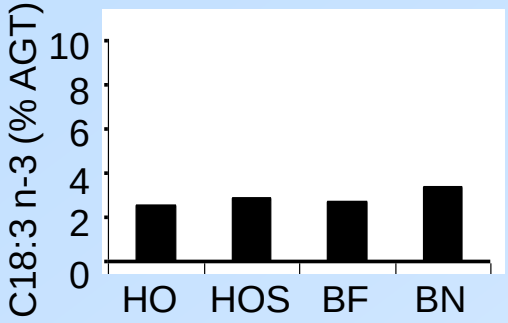
(% Total FA)

Thèse d'Hélène Ezanno (2012)

Saturates and PUFAs bioavailability

C18:3 n-3

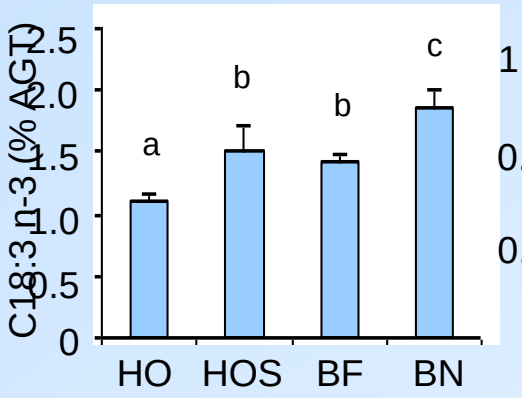
Régimes



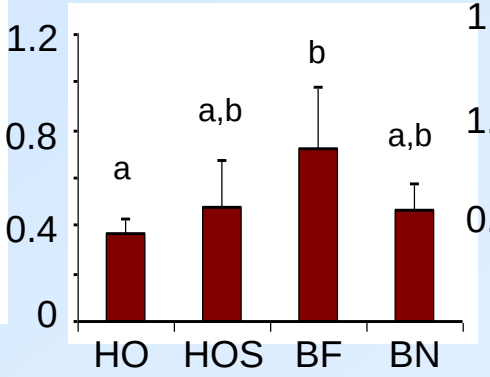
$$18{:}3 \xrightarrow{\Delta 6} 18{:}4 \xrightarrow{\varepsilon} 20{:}4 \xrightarrow{\Delta 5} 20{:}5 \xrightarrow{\varepsilon} 22{:}5 \xrightarrow{\varepsilon} 24{:}5 \xrightarrow{\Delta 6} 24{:}6 \xrightarrow{\beta} 22{:}6 \quad \text{n-3}$$

⊕ **Butter**

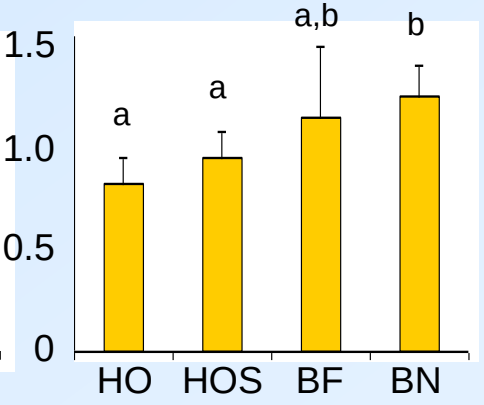
Adipose Tissu



Liver

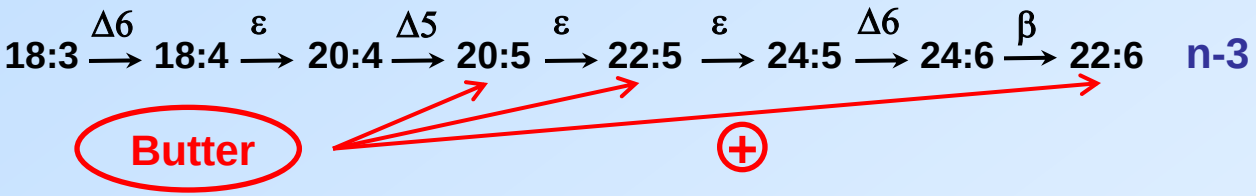


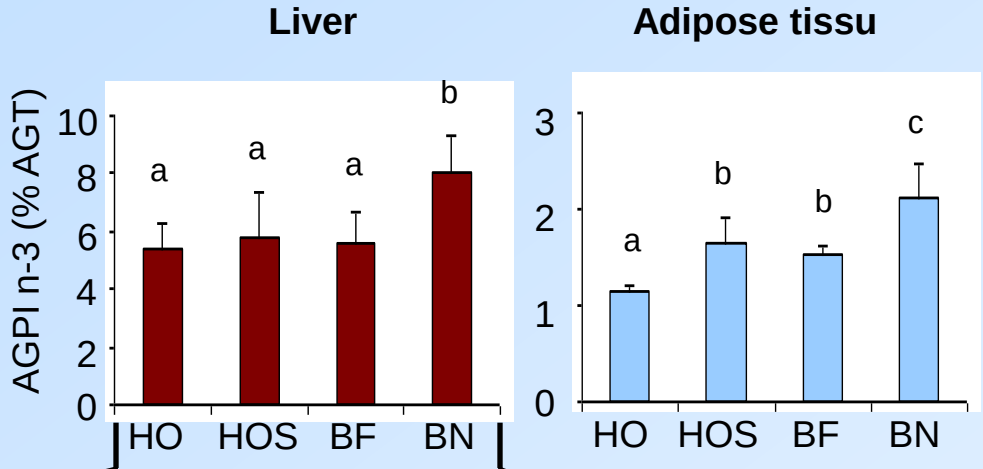
Plasma

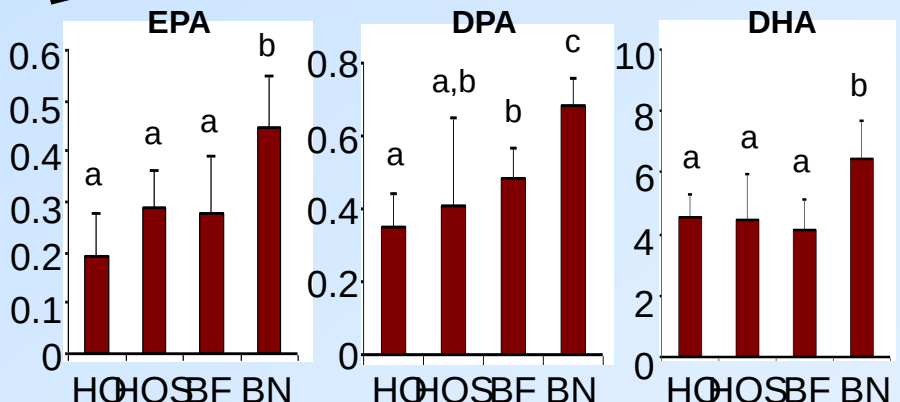


Saturates and PUFAs bioavailability

LC-PUFAs n-3

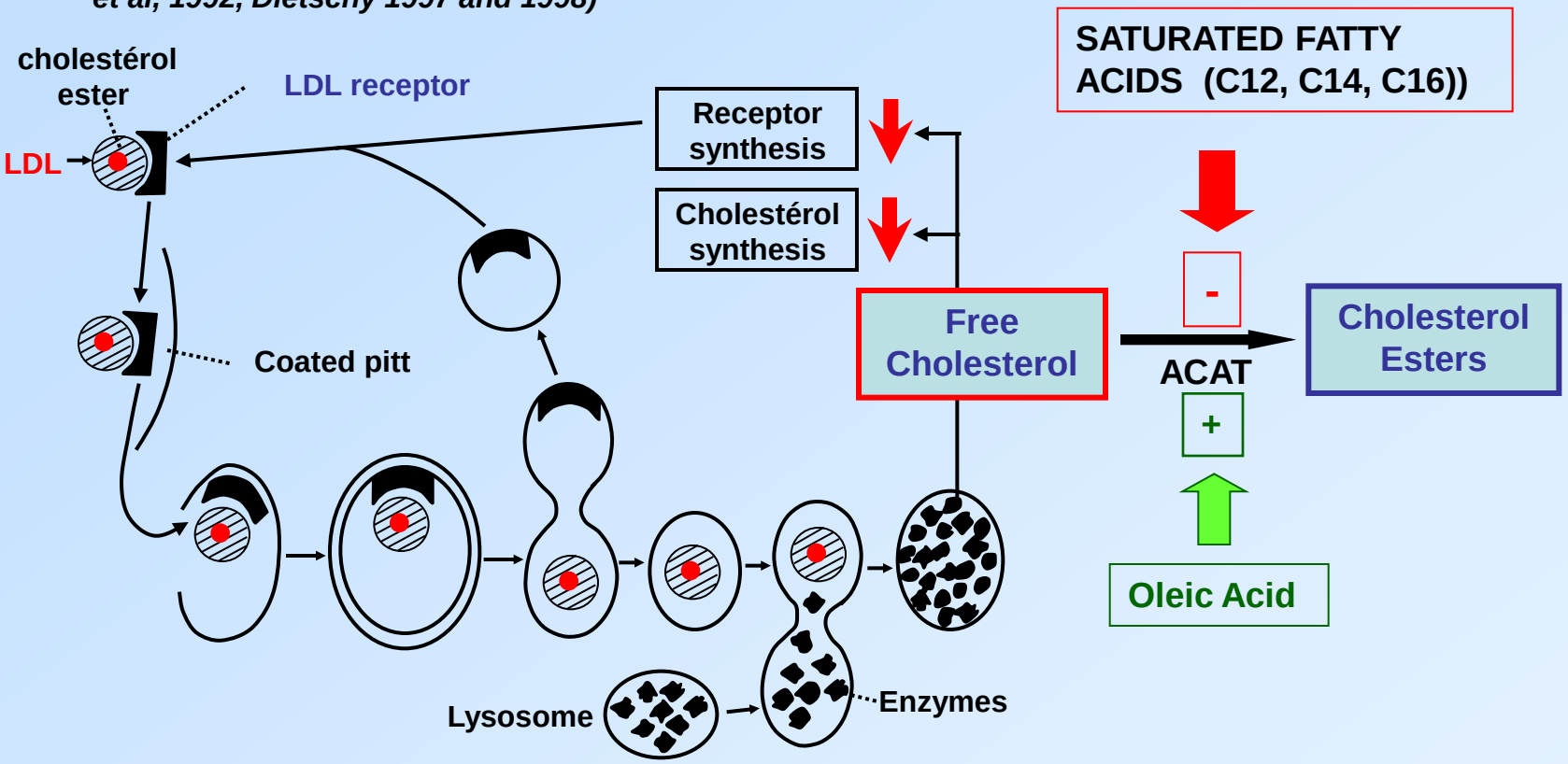






Saturated Fatty acids and cholesterolemia (C12:0, C14:0, C16:0)

- Decrease LDL clearance by decrease of LDL-receptor transcription (SREBP-1) *(Woollett et al, 1992, Dietschy 1997 and 1998)*

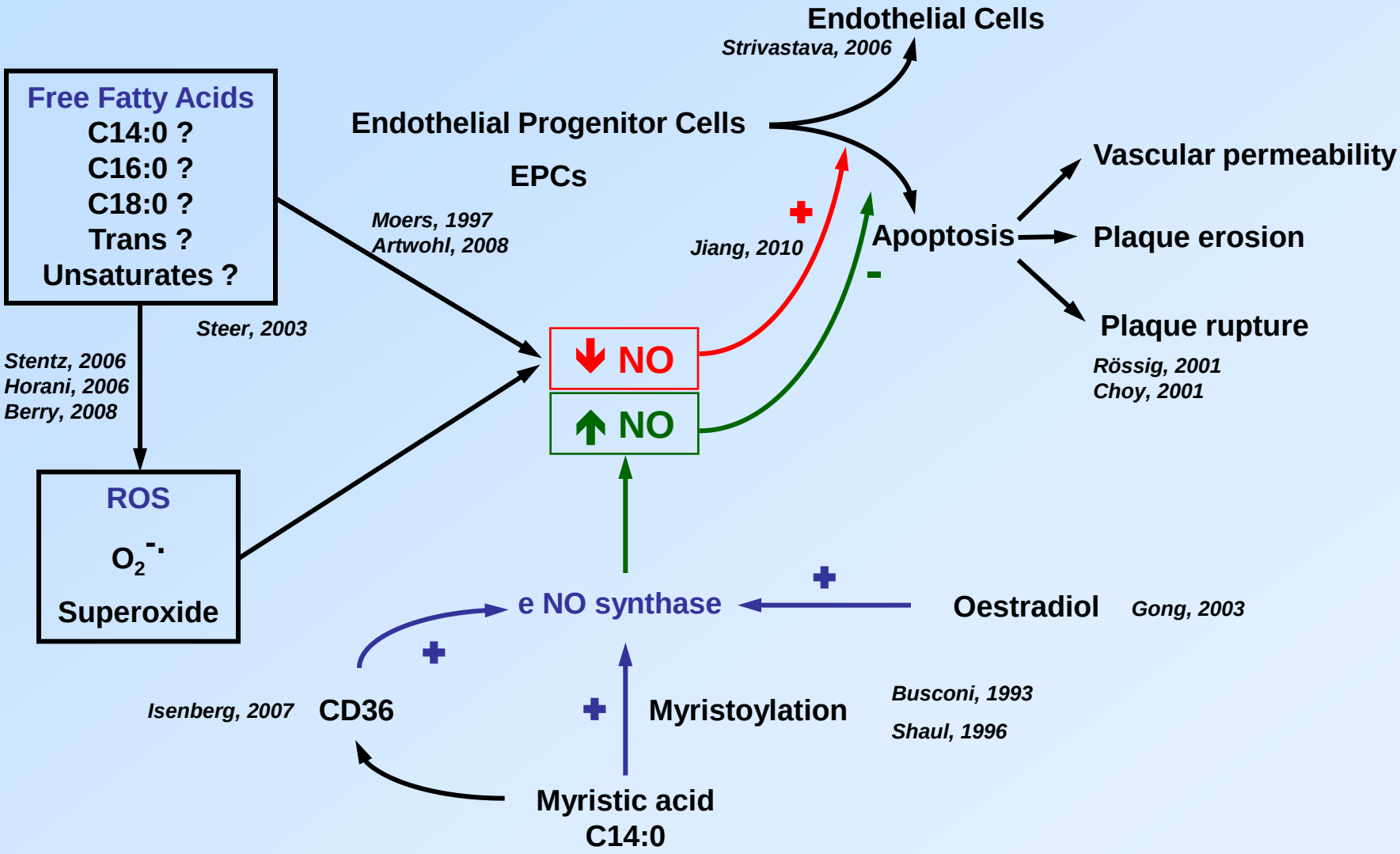


- Increase VLDL secretion by inhibition of apo-B dégradation *(Kummrow et al, 2002)*

INCREASE OF LDL-CHOLESTEROL (dose-dependent),

be carefull about small and dense LDL *(Katan 1995)*

Vascular endothelium



No data really specific to SFA and or to dietary SFA (meaning fructose/glucose load may be worse)