SATURATED FATTY ACIDS :
METABOLISM, FUNCTIONS, RECOMMANDATIONS

And what about Palm Oil ?

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SATURATED FATTY ACIDS

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

Sugars, starch.....

\[
\begin{align*}
\text{Mammary gland} & : \\
& \quad \text{C4} \\
& \quad \text{C6} \\
& \quad \text{C8} \\
& \quad \text{C10} \\
& \quad \text{C12} \\
& \quad \text{C14}
\end{align*}
\]

Palmitic acid 16:0
SATURATED FATTY ACIDS

- We make them
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- Problems with CVD and MS biomarkers
<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids (g/day)</td>
<td>103,0</td>
<td>81,6</td>
<td>91,8</td>
</tr>
<tr>
<td>Lipids (%Energy)</td>
<td>38,8</td>
<td>39,8</td>
<td>39,3</td>
</tr>
<tr>
<td>Saturated Fatty Acids (%En)</td>
<td>15,8</td>
<td>15,9</td>
<td>15,9</td>
</tr>
</tbody>
</table>

AET : Apport énergétique total

Source: INCA 2
SATURATED FATTY ACIDS

- We make them
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Comparative absorption of saturated fatty acids

Intestine

Long chain fatty acids → Chylomicrons → Lymph → Circulation

Short and middle chain fatty acids → Portal vein → Catabolism (β-oxidation)

Adipose → Storage

Muscle → Storage

Liver
Myristic / Palmitic acid metabolism

C14:0

Uptake

Incorporation into lipids

β-oxidation

Desaturation

Elongation

Acylation of proteins (myristoylation)

Gene regulation ?

Secretion

HEPATOCYTE

Biosynthesis

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),
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 $\beta$-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, palmitic acid accumulates in the cell!
Stearic acid is less synthesized (than palmitic), actively desaturated into oleic acid. No accumulation!
SATURATED FATTY ACIDS

- We make them
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Myristic / Palmitic acid specific acylation function

C14:0

Uptake

Incorporation into lipids

β-oxidation

Elongation

Desaturation

Acylation of proteins

Gene regulation ?

Biosynthesis

Secretion

HEPATOCYTE

P. Legrand
N-terminal myristoylation

myristoyl-CoA

myristoylated protein

membrane association

subcellular localization

protein-protein interaction

protein activation
Myristoylation and palmitoylation of the $\alpha$-subunit of heterotrimeric G proteins

N-terminus: G C T L S A E D K A A V E R-

myristic acid  \[ \text{C 14:0} \] palmitic acid

$\alpha$  \[ \text{C 16:0} \]

$\beta \gamma$

GDP

Wedegaertner, 1998
TWO EXAMPLES OF MYRISTIC ACID EFFECT (in relation to myristoylation)

- Activation of conversion of C18:3 n-3 and C18:2 n-6 towards long chain derivatives

- Activation of sphingolipids synthesis (ceramide)
Effect of myristic acid on PUFAs composition in the rat *in vivo* and in human

\[ \Delta 6 \]

14:0 → 16:1 → 16:2 → 18:2 → 18:3 → 20:3 → 20:4

16:0 → 16:1 → 16:2 → 18:2 → 18:3 → 20:3 → 20:4

18:0 → 18:1 → 18:2 → 20:2 → 20:3

18:0 → 18:1 → 18:2 → 20:2 → 20:3

18:2 → 18:3 → 20:3 → 20:4

18:3 → 18:4 → 20:4 → 20:5 → 22:5

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

Brain and red blood cells

P. Legrand
TWO EXAMPLES OF MYRISTIC ACID EFFECT
(in relation to myristoylation)

- Activation of conversion of C18:3 n-3 and C18:2 n-6 towards long chain derivatives

- Activation of sphingolipids synthesis (ceramide)
Importance of SFA for sphingolipids biosynthesis in animals

Palmitic acid + serine → 3-cetosphinganine → sphinganine → de novo biosynthesis

Saturated fatty acid → sphinganine

Dihydroceramide Δ4-desaturase is myristoylated

Ceramide 1-P → sphingosine 1-P → sphingosine

Ceramide → phosphosphingolipids

Glycosphingolipids

Beauchamp et al., 2007
Saturated fatty acids functions at a glance
(in addition to energetical function)

- Inhibition of tumor proliferation \textit{in vivo} and \textit{in vitro}
- Induction of apoptosis
- Less fat deposition
- Colon and smooth muscle cells
- C8 $\downarrow$ VLDL secretion (inhibition of apo B synthesis)
- Hypocholesterolemic effect (C8, C10)
- Antiviral role

- Specific acylation of proteins
- Activation of conversion from C18:3 n-3 towards EPA + DHA
- Activation of sphingolipids synthesis
Saturated fatty acids functions at a glance
(in addition to energetical function)

- Active desaturation to oleic acid
- Nervous structure (myelinisation)
- Componant of sphingolipids
- 1/3 of phospholipids fatty acids - structural role
- Non specific acylation of some proteins
- Low elongation et β-oxidation
- Nervous structure (myelinisation)
SATURATED FATTY ACIDS

- We make them
- We eat them
- Metabolism
- Important specific functions
- **Problems with CVD and MS biomarkers**
Saturated fatty acids functions

Problems?

\[ \begin{align*}
    & C4 \quad \text{butyric} \\
    & C6 \quad \text{caproïc} \\
    & C8 \quad \text{caprylic} \\
    & C10 \quad \text{capric} \\
    & \textcolor{red}{C12} \quad \text{lauric} \\
    & C14 \quad \text{myristic} \\
    & \textcolor{red}{C16} \quad \text{palmitic} \\
    & C18 \quad \text{stearic} \\
    & C20 \quad \text{arachidic} \\
    & C22 \quad \text{behenic} \\
    & C24 \quad \text{lignoceric}
\end{align*} \]

Problem with the CVD risk:
Deleterious effects \textcolor{red}{\ldots \text{in case of excess}}

Accumulation of palmitic acid: endogenous + exogenous origins

- No problem with the CVD risk!
Saturated fatty acids and health

At the beginning: association with CHD risk

Keys 1966, Kato 1973

But: ecological studies (7 countries study)

NEVER CONFIRMED BY COHORT STUDIES
Association between SFA and CVD risk:

**Neutral**
- Shekelle 1981
- Kushi 1985
- Posner 1991
- Ascherio 1996
- Pietinen 1997
- 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"

For dairy products specifically, see works by Elwood et al: no risk association
- NO HYPERCHOLESTEROLEMIC EFFECT OF SHORT AND MIDDLE CHAIN SFA

  *Hu at al. 1999*

- NO HYPERCHOLESTEROLEMIC EFFECT OF STEARIC ACID

  *Kelly et al. 2001, Yu et al. 1995, Mensink 2005*

- ATHEROGENIC SFA IN CASE OF EXCESS: C16, C14, C12,

  *Kris-Etherton and Yu 1997*
Physiopathological mechanisms?

- Circulating lipids (LDL-cholesterol)
- Metabolic syndrome, insulin resistance
- Endothelial function
- Coagulation-fibrinolysis
- ............
CONCLUSION, Take Home Messages

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.

- Need of more precise epidemiological studies (different saturated fatty acids, dose-effects approach, controls…) for evaluating the levels and sources where C16, (C14, C12) fatty acids are deleterious

- Time for “up to date” recommendations without caricatural old statements of toxicity or eviction……..
..........  So, we did it in France throw the recommendaions of the food safety agency (ANSES)
ANC : NON ESSENTIAL FA : SATURATED FA

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

<table>
<thead>
<tr>
<th>NON ESSENTIAL FA</th>
<th>Minimal physiological requirement</th>
<th>Metabolic syndrome, diabetes, obesity</th>
<th>Cardiovascular diseases</th>
<th>Cancers : breast, colon</th>
<th>Neuro-psychiatric pathologies</th>
<th>Other pathologies : Macular degeneration</th>
<th>ANC 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lauric acid (C12:0) + myristic acid (C14:0) + palmitic acid (C16:0)</td>
<td>-</td>
<td>-</td>
<td>≤ 8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>≤ 8</td>
</tr>
<tr>
<td>Total Saturated FA</td>
<td>-</td>
<td>-</td>
<td>≤ 12</td>
<td>≤ 12</td>
<td>-</td>
<td>-</td>
<td>≤ 12</td>
</tr>
<tr>
<td>Oleic acid C18:1 n-9</td>
<td>-</td>
<td>-</td>
<td>≤ 20</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15 - 20</td>
</tr>
<tr>
<td>Others non essential FA</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

- Lack of coherent data
- Value obtained from epidemiological association studies, in the absence of intervention studies.
- Data obtained from breast cancer only
And Palm Oil in Nutrition?
### Fatty acid Composition of Milk, Palm and Coco Lipids

#### % total fatty acids

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Milk</th>
<th>Palm</th>
<th>Coco</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4:0</td>
<td>3-4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C6:0</td>
<td>2-3</td>
<td>-</td>
<td>&lt;1</td>
</tr>
<tr>
<td>C8:0</td>
<td>1-2</td>
<td>-</td>
<td>6-10</td>
</tr>
<tr>
<td>C10:0</td>
<td>2-4</td>
<td>-</td>
<td>5-10</td>
</tr>
<tr>
<td>C12:0</td>
<td>3-4</td>
<td>&lt;0.2</td>
<td>39-54</td>
</tr>
<tr>
<td>C14:0</td>
<td>9-12</td>
<td>1-2</td>
<td>15-23</td>
</tr>
<tr>
<td>C16:0</td>
<td>23-32</td>
<td>43-46</td>
<td>6-11</td>
</tr>
<tr>
<td>C16:1 n-7</td>
<td>2-3</td>
<td>&lt;0.3</td>
<td>&lt; 2</td>
</tr>
<tr>
<td>C18:0</td>
<td>13</td>
<td>4-6</td>
<td>1-4</td>
</tr>
<tr>
<td>C18:1 n-9</td>
<td>2</td>
<td>37-41</td>
<td>4-11</td>
</tr>
<tr>
<td>C18:2 n-6</td>
<td>2</td>
<td>9-12</td>
<td>1-2</td>
</tr>
<tr>
<td>C18:3 n-3</td>
<td>&lt; 1</td>
<td>&lt;0.4</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>SFA</td>
<td>56-74</td>
<td>48-54</td>
<td>71-100</td>
</tr>
</tbody>
</table>
Evolution of diet habits:
- Increase of processed food, biscuits…
- Palm oil Incorporation in these food.

<table>
<thead>
<tr>
<th></th>
<th>1960</th>
<th>1990</th>
<th>2000</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consumption</td>
<td>0.2</td>
<td>0.4</td>
<td>1.8</td>
<td>2.2</td>
</tr>
<tr>
<td>(kg/person/an)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Palm oil: 6 g/day
6% total lipids (100g/d)

Saturates from palm oil: 3 g/day
8.5% total saturated (30-40 g/d)

Part of palmitic Al (adequate intake): 17 % Al (17 g/d)

Evolution of palm oil consumption in France

Origin: Agreste, others: 1 kg/an
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)...
Predicted changes (Δ) in the ratio of serum total to HDL cholesterol when mixed fat constituting 10% of energy in the “average” US diet is replaced isoenergetically with a particular fat or with carbohydrates.
Palm Oil Consumption
and Saturated fatty acids from this source

- **No toxicity at all, obviously**

- **No real problem but hard to defend and not to increase anyway:**

- **We want to decrease palmitic acid in the diet and palm oil is one of the richest source!**

- **Its hidden and cheap, so..... Uncontrolled**

  **Limited place in the diet ....**
Thanks for your attention

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

INCREASE OF LDL-CHOLESTEROL (dose-dependent), be careful about small and dense LDL (Katan 1995)
MECANISM OF INSULIN RESISTANCE (muscle, adipose)

- **Tetrameric Glycoprotein**
- **Glucose GLUT4 translocation**
- **PI$_3$ kinase**
- **IRS-tyr-P**
- **IRS-Ser-P**
- **Acyl CoAs (free fatty acids), diacylglycerols ; LIPOTOXICITY**
- **Pro inflammatory Cytokins (IL1, TNF$_\alpha$)**
- **Insulin in excess**

**Girard, 2005; Capeau, 2005**