Les Hôpitaux Universitaires de STRASBOURG

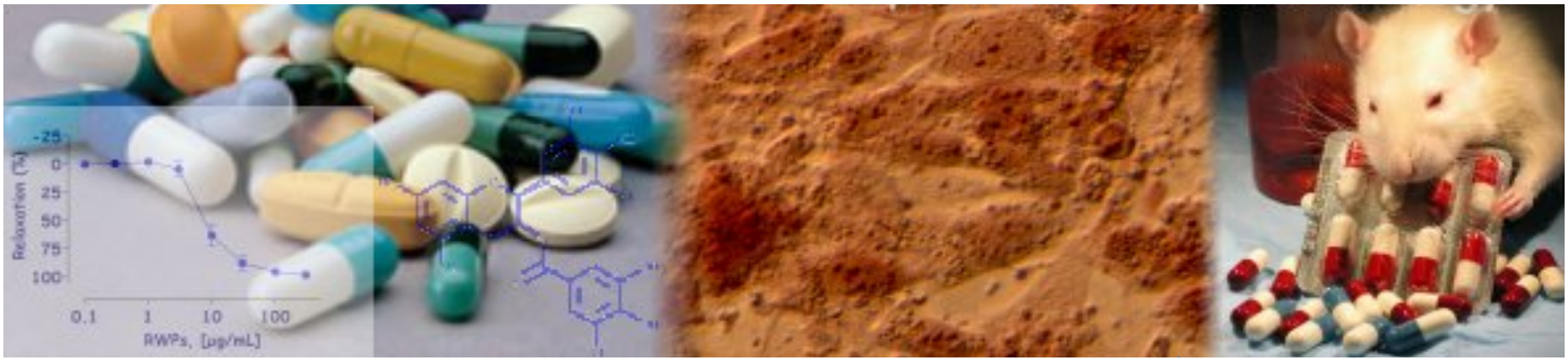
UNIVERSITÉ DE STRASBOURG

# Émulsions lipidiques en réanimation

Cours DESC juin 2018

J. Helms

Réanimation Médicale – NHC



# Problématiques

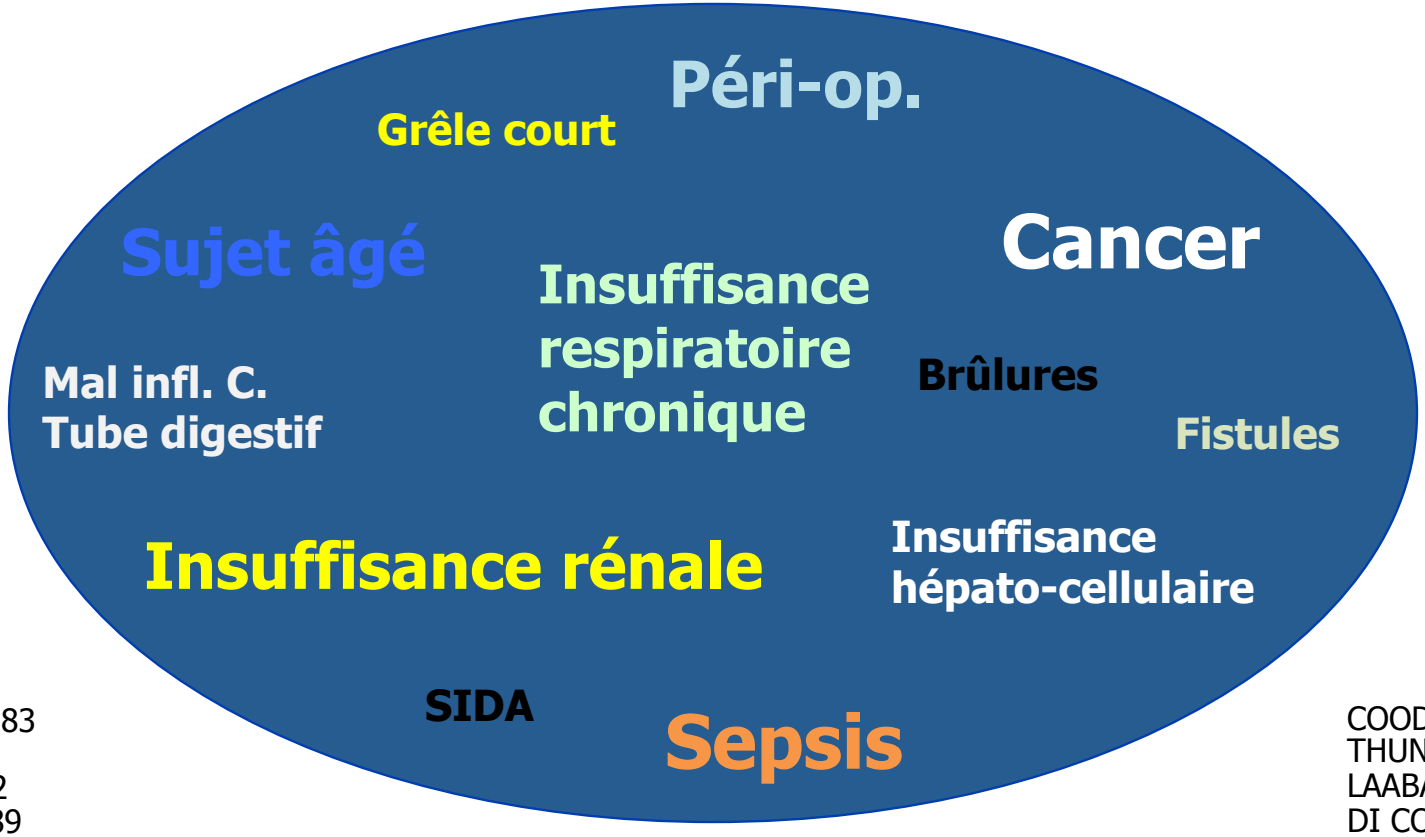
1. Dénutrition et agression
2. Nutrition et immunonutrition
3. Indications et timing de la NP
4. Choix de l'émulsion lipidique
5. Et en pratique ??

# 1) DÉNUTRITION ET AGRESSION

# Dénutrition

30 à 50 % des patients hospitalisés

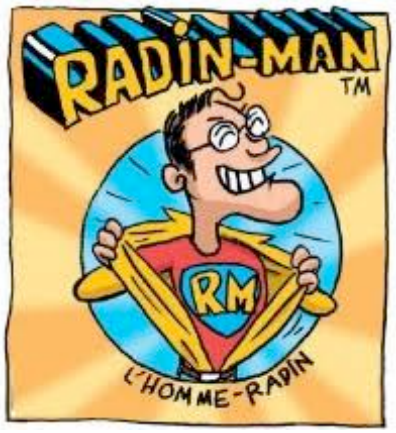
**45% des patients de réanimation**




JOUQUAN; 1983
REILLY; 1988
PERROT; 1982
RIETSCH; 1989

COODLEY; 1994
THUNBERG; 1981
LAABAN; 1993
DI COSTANZO; 1987
DALY; 1990

# Les patients de réanimation sont sous-alimentés




- 80 % des calories requises sont prescrites
  - 70 % des calories sont effectivement reçues
  - 50 % des malades de réanimation reçoivent <70% des calories nécessaires

**Apports recommandés 25 à 35 Kcal/kg/j**

# Dénutrition : facteur prédictif indépendant de mortalité

| Independent variables | *P* value | OR (95%CI) |
|---|---|---|
| BMI | | |
| 18.5–24.9 | | 1 |
| <18.5 | 0.01 | 1.63 (1.11–2.39) |
| 25–29.9 | 0.053 | 0.75 (0.56–1.004) |
| >30 | 0.01 | 0.60 (0.40–0.88) |
| Admission diagnosis COPD | 0.005 | 0.51 (0.32–0.82) |

**Body mass index**

**An additional prognostic factor in ICU patients**

Intensive Care Med (2004) 30:437–443

# Dénutrition chronique vs. aiguë

Dénutrition chronique

(défaut d'apport)

Comportement de jeûne prolongé

Cachexie progressive

Dénutrition aiguë

Augmentation des besoins

(état d'agression)

Hypermétabolisme

Auto-cannibalisme

# Complications de la dénutrition

Réduction de la masse protéique

**TROUBLES TROPHIQUES**

**↓ IMMUNITE CELLULAIRE**

**↓ FORCE MUSCULAIRE**

COMPLICATIONS CICATRISATION

INFECTIONS

LESIONS PULMONAIRES
↓ FORCE DIAPHRAGM.

**MORBIDITE**

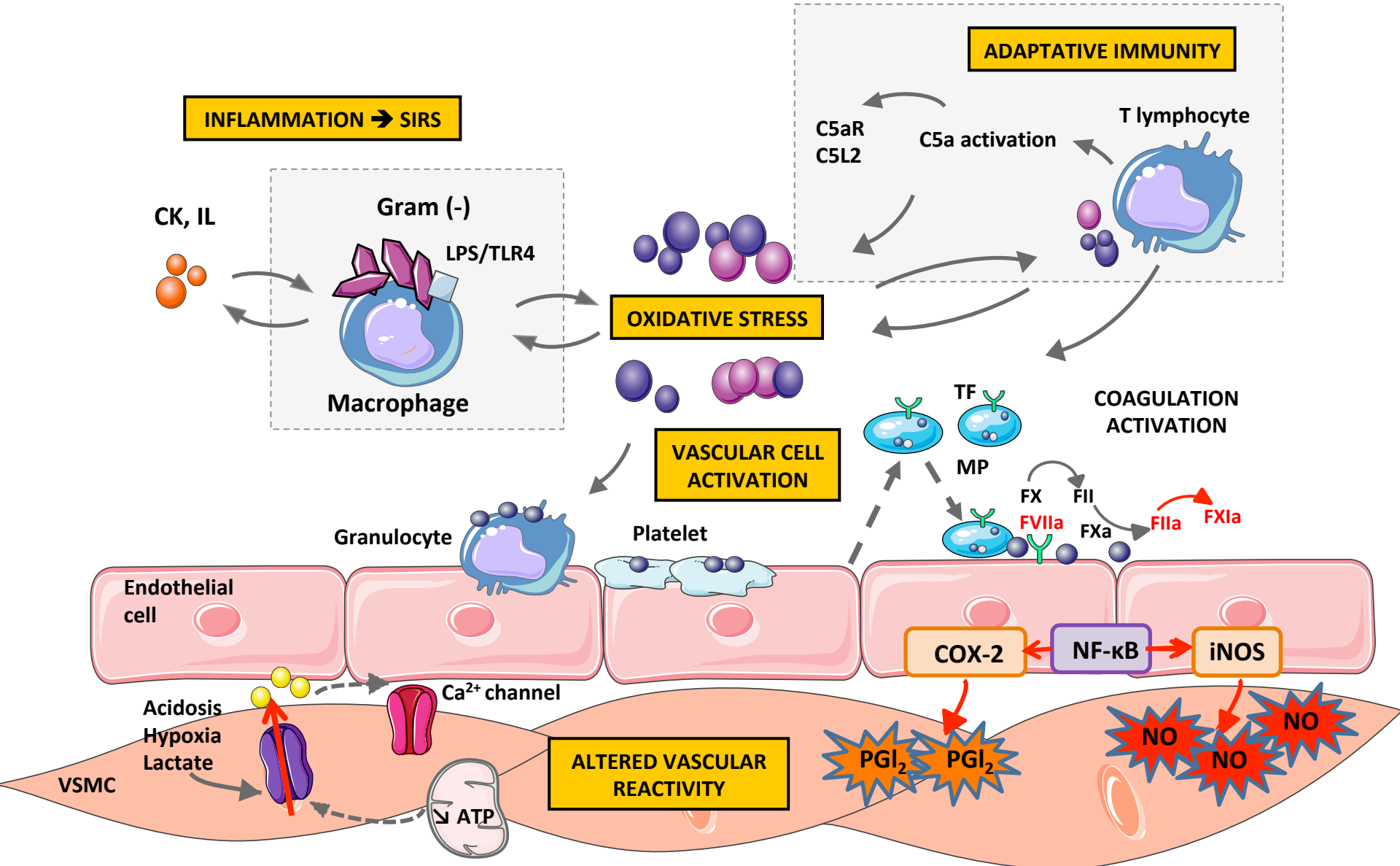
DETSKY; 1987
BUZBY; 1980
WARNOLD; 1984
DI COSTANZO; 1995

# La dénutrition : facteur de comorbidité

## COMPLICATIONS GRAVES

| | NON DENUTRIS | DENUTRIS | p |
|---|---|---|---|
| Braga (440) | 14 % | 31 % | p < 0,001 |
| Mullen (145) | 16 % | 42 % | p < 0,001 |
| Veterans Affairs | 24 % | 43 % | p < 0,001 |

# Physiopathologie de l'agression



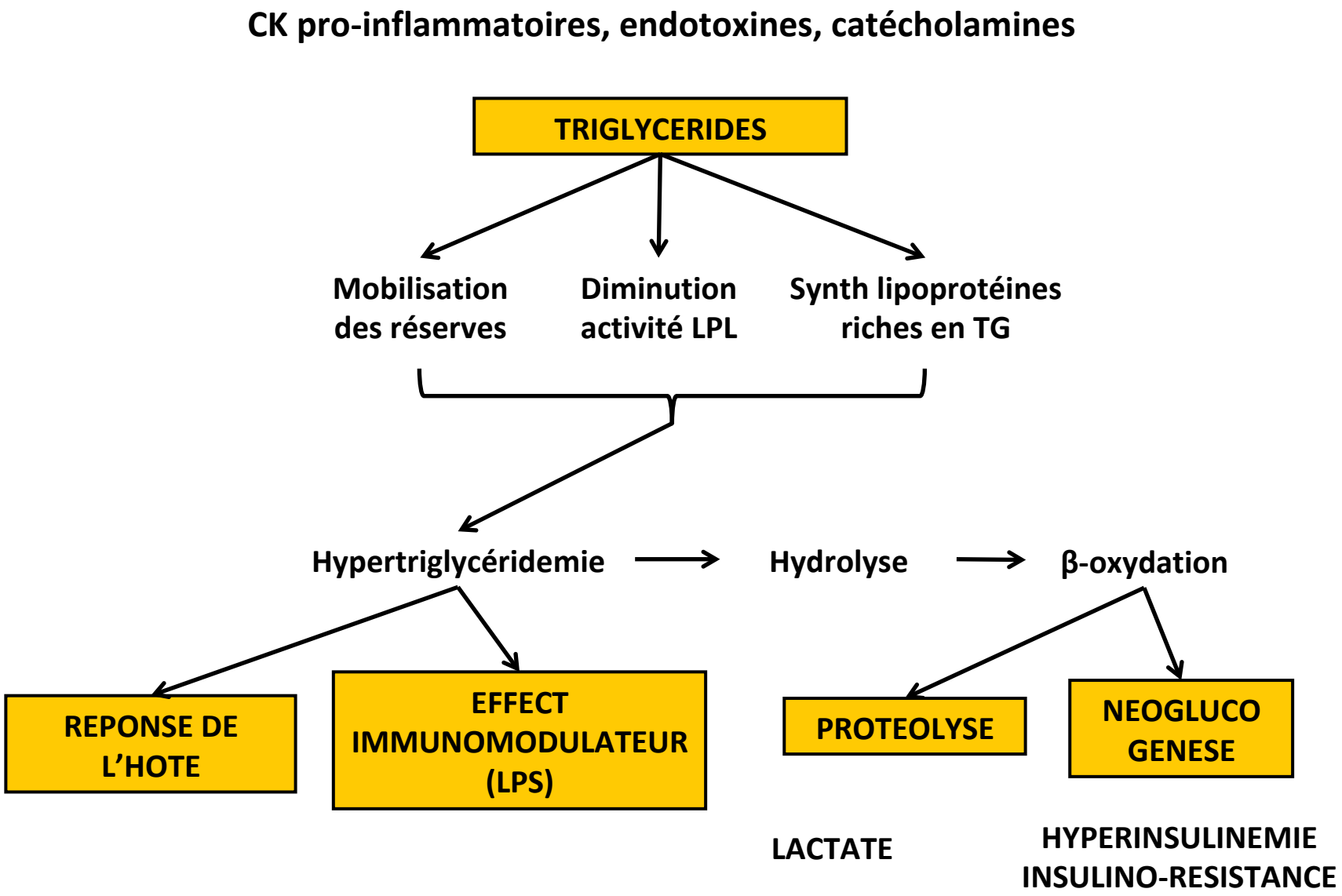
# Métabolisme et stress aigu

- 1ère phase : J1-J2
  - **Diminution de tous les métabolismes**
  - **Hyperglycémie** par **mobilisation des réserves** endogènes (muscles, foie)

- 2ème phase : durée et intensité variables
  - **Hypercatabolisme** (muscles, foie) : AG stockés, protéines
  - Néoglucogenèse, insulino-résistance
  - Lipolyse

- 3ème phase : **phase anabolique** de récupération.

# Adaptation du métabolisme lipidique



# 2) NUTRITION ET IMMUNONUTRITION

# Enjeux de la nutrition artificielle de l'agressé

**Contrôle de la réponse métabolique à l'agression**

- Prévenir la dénutrition
- Supporter la fonction des organes défaillants
- Moduler la fonction immunitaire et la réponse inflammatoire : « immunonutrition »


# Immunonutrition ?

- Ajout de nutriments spécifiques destinés à améliorer les fonctions immunitaires
  - en quantité supérieure à la normale
  - dans la NE ou NP
- Relation étroite état nutritionnel / immunité

# 3) INDICATIONS ET TIMING DE LA NUTRITION PARENTÉRALE

# Indications de la nutrition parentérale

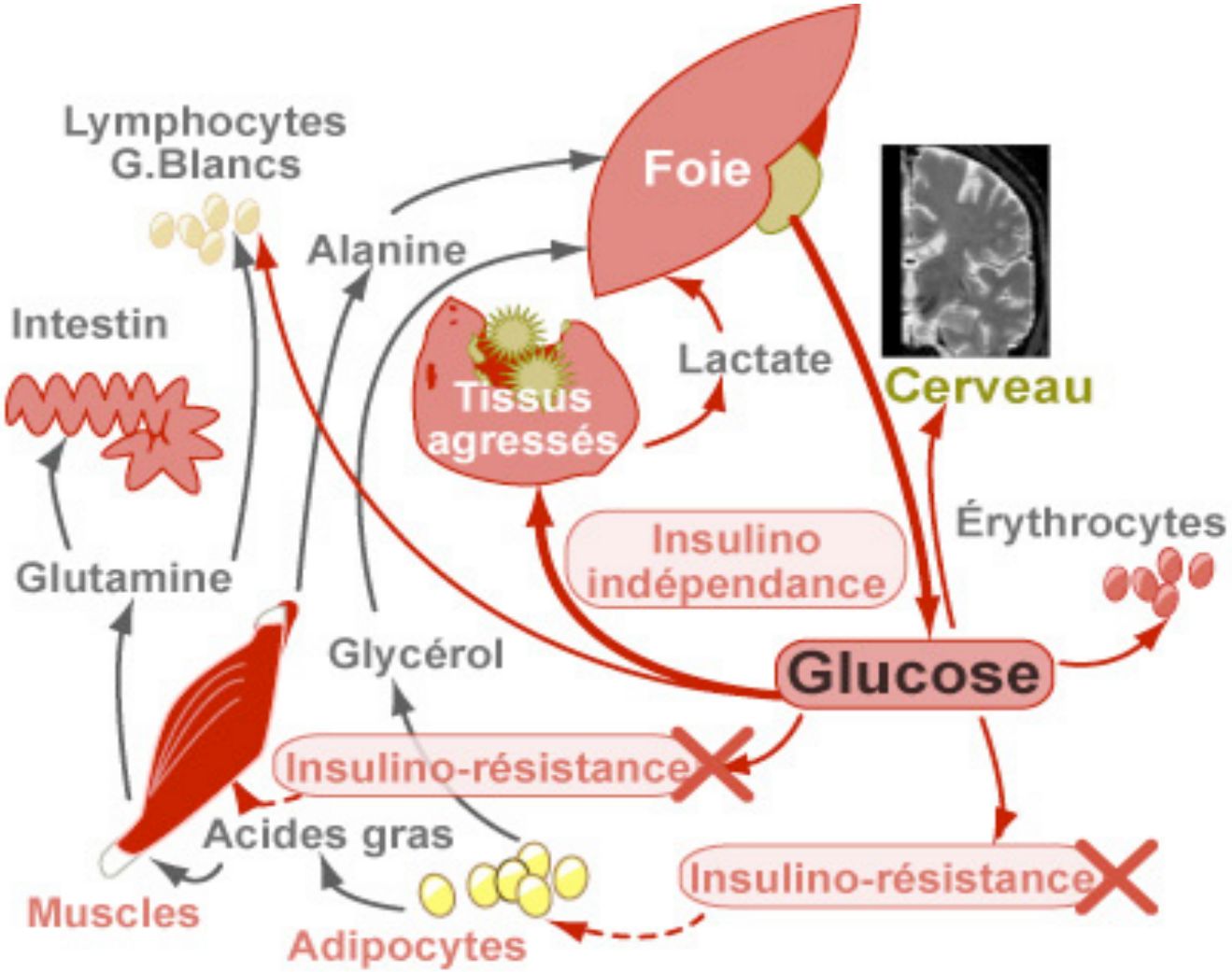
- **Partielle :**
  - En complément voie orale / entérale
  - et situation d'hypermétabolisme > 7-10 j.

- **Totale :** impossibilité d'alimentation orale ou entérale

MAIS :

- Moins physiologique
- Coûteuse
- Complications potentielles

# Timing : à la phase aiguë ?




- état de choc
- catécholamines
- curarisation

- Néoglucogenèse hépatique
- Hypercatabolisme
- Mobilisation des réserves lipidiques

*Pr Hasselmann*

# Timing : à la phase aiguë ?

- **CONTRE : restriction protéino-énergétique**
  - ↘ thermogenèse
  - ↘ production d'urée
  - ↘ turn-over du glucose
  - ne majore pas la protéolyse.

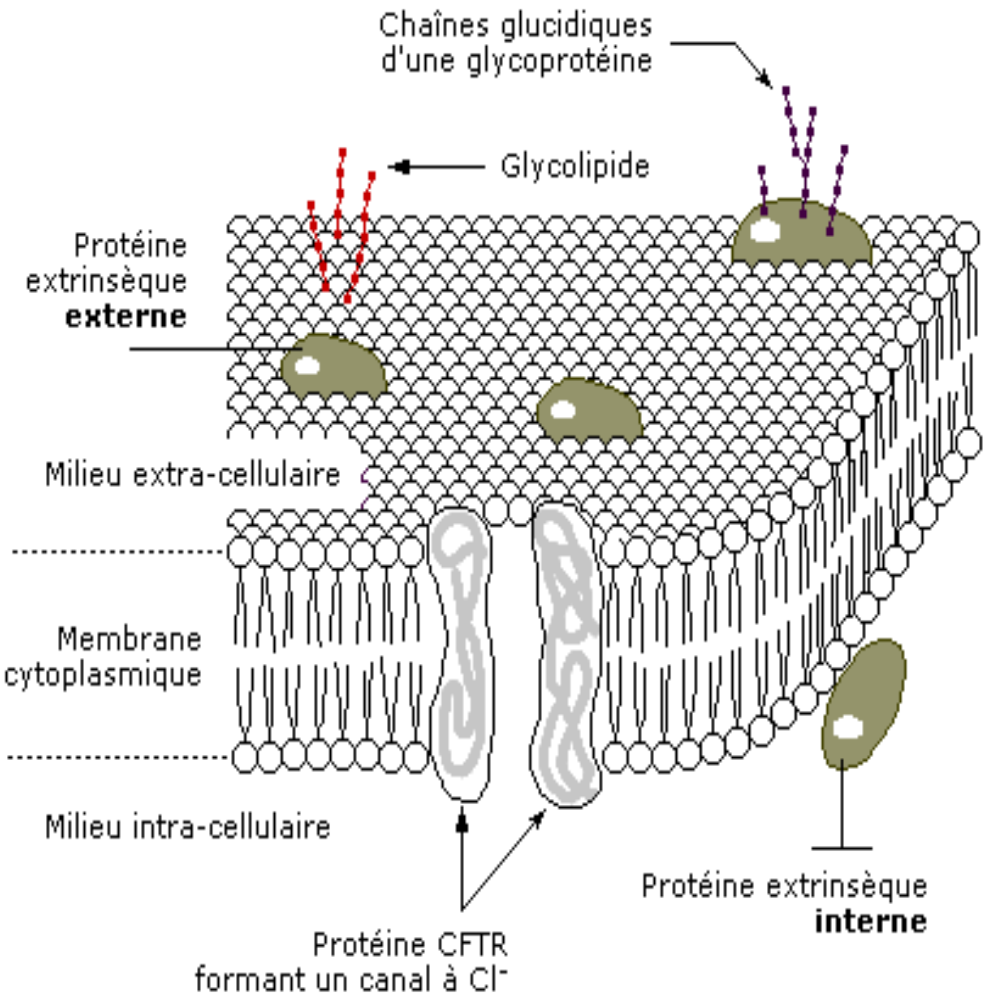
- **POUR : en l'absence d'apports adéquats, mobilisation des réserves**
  - dépenses énergétiques
  - synthèses protéiques "prioritaires »
  - épuisement du stock d'éléments traces / vitamines
  - **immunonutrition ?** haute concentration de n-3 (poisson) dans le SIRS ↘ mortalité, infections acquises, durée de séjour

# 4) CHOIX DE L'ÉMULSION LIPIDIQUE

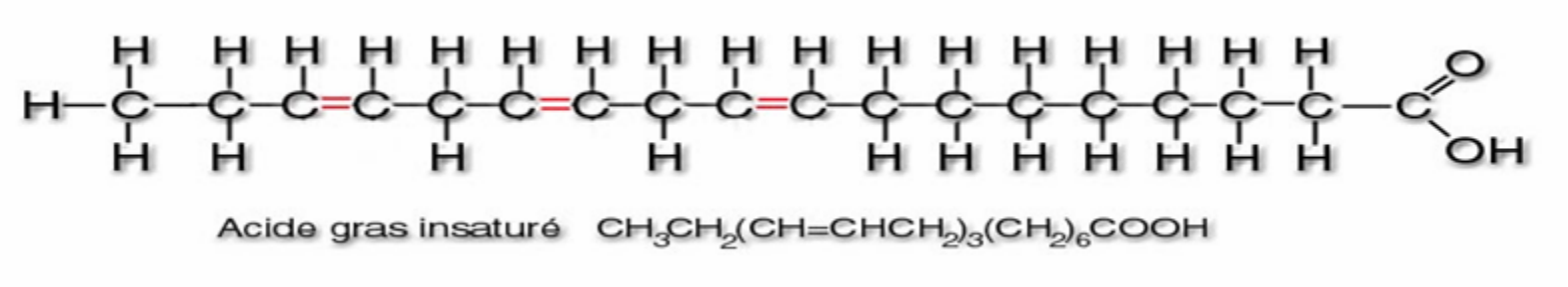
# Les lipides

3 rôles :

- **Énergétique** : 9 kcal/g
- **Structural :** mb
- **Fonctionnel :** PG, TX, LT, lipoprotéines…

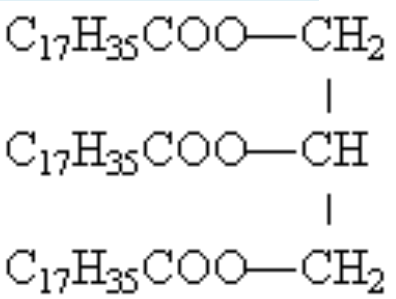


# Nomenclature : les lipides




**Acide alpha linolénique (18:2 n-3)**

- Grosses molécules => nombreux C, reliés par liaisons simples ou doubles
  - Selon nb de doubles liaisons : AGS / AGMI / AGPI
  - N-x : x = position de la 1ère double liaison par rapport à l'extrémité C-terminale
- 3 AG = TG
  - TCM / TCL en fonction du nombre de C (14)



# Émulsions lipidiques en réanimation

- **Apport calorique** / faible charge osmotique

- TG émulsifiés par des phospholipides :
  - Triglycérides à chaines longues : TCL
  - Triglycérides à chaines moyennes : TCM

- Propriétés des émulsions dépendent de :
  - Qualité AG
  - Ratio AG (oméga 3, oméga 6, oméga 9…)

# Émulsions lipidiques en réanimation

Historiquement :

- TCL (soja) n-6 (acide linoléique 18:2) = Intralipide
  <=> AGPI essentiels


- TCL / TCM : 1/1

- Puis
  - n-3 (poisson) = Omegaven
  - n-9 (olive) = Oliclinomel
  - TCM complexes de synthèse (Structolipide)
  - Les mélanges (Lipidem, Medialipide, Clinoleic, SMOF…)

# Composition des émulsions

| | TCL (soja) | TCM (coco) | n-3 (poisson) | n-9 (olive) |
|---|---|---|---|---|
| Intralipide | 20 | 0 | 0 | 0 |

# Composition des émulsions

| | TCL (soja) | TCM (coco) | n-3 (poisson) | n-9 (olive) |
|---|---|---|---|---|
| Intralipide | 20 | 0 | 0 | 0 |
| Médialipide | 10 | 10 | 0 | 0 |

# Composition des émulsions

| | TCL (soja) | TCM (coco) | n-3 (poisson) | n-9 (olive) |
|---|---|---|---|---|
| Intralipide | 20 | 0 | 0 | 0 |
| Médialipide | 10 | 10 | 0 | 0 |
| Omégaven | 0 | 0 | 20 | 0 |

# Composition des émulsions

| | TCL (soja) | TCM (coco) | n-3 (poisson) | n-9 (olive) |
|---|---|---|---|---|
| Intralipide | 20 | 0 | 0 | 0 |
| Médialipide | 10 | 10 | 0 | 0 |
| Omégaven | 0 | 0 | 20 | 0 |
| Clinoléic | 4 | 0 | 0 | 16 |

# Composition des émulsions

| | TCL (soja) | TCM (coco) | n-3 (poisson) | n-9 (olive) |
|---|---|---|---|---|
| Intralipide | 20 | 0 | 0 | 0 |
| Médialipide | 10 | 10 | 0 | 0 |
| Omégaven | 0 | 0 | 20 | 0 |
| Clinoléic | 4 | 0 | 0 | 16 |
| Lipidem | 8 | 10 | 2 | 0 |

# Composition des émulsions

| | TCL (soja) | TCM (coco) | n-3 (poisson) | n-9 (olive) |
|---|---|---|---|---|
| Intralipide | 20 | 0 | 0 | 0 |
| Médialipide | 10 | 10 | 0 | 0 |
| Omégaven | 0 | 0 | 20 | 0 |
| Clinoléic | 4 | 0 | 0 | 16 |
| Lipidem | 8 | 10 | 2 | 0 |
| SMOF | 6 | 6 | 3 | 5 |

# PROPRIÉTÉS DES ACIDES GRAS ET MÉCANISMES D'ACTION IN VIVO

# Omega 6 vs. Omega 3 ?

Linoleic acid (18:2n-6) —Δ15-desaturase (Plants only)→ α-Linolenic acid (18:3n-3)

Linoleic acid (18:2n-6) —Δ6-desaturase→ γ-Linolenic acid (18:3…

α-Linolenic acid (18:3n-3) —Δ6-desaturase→ Stearido…

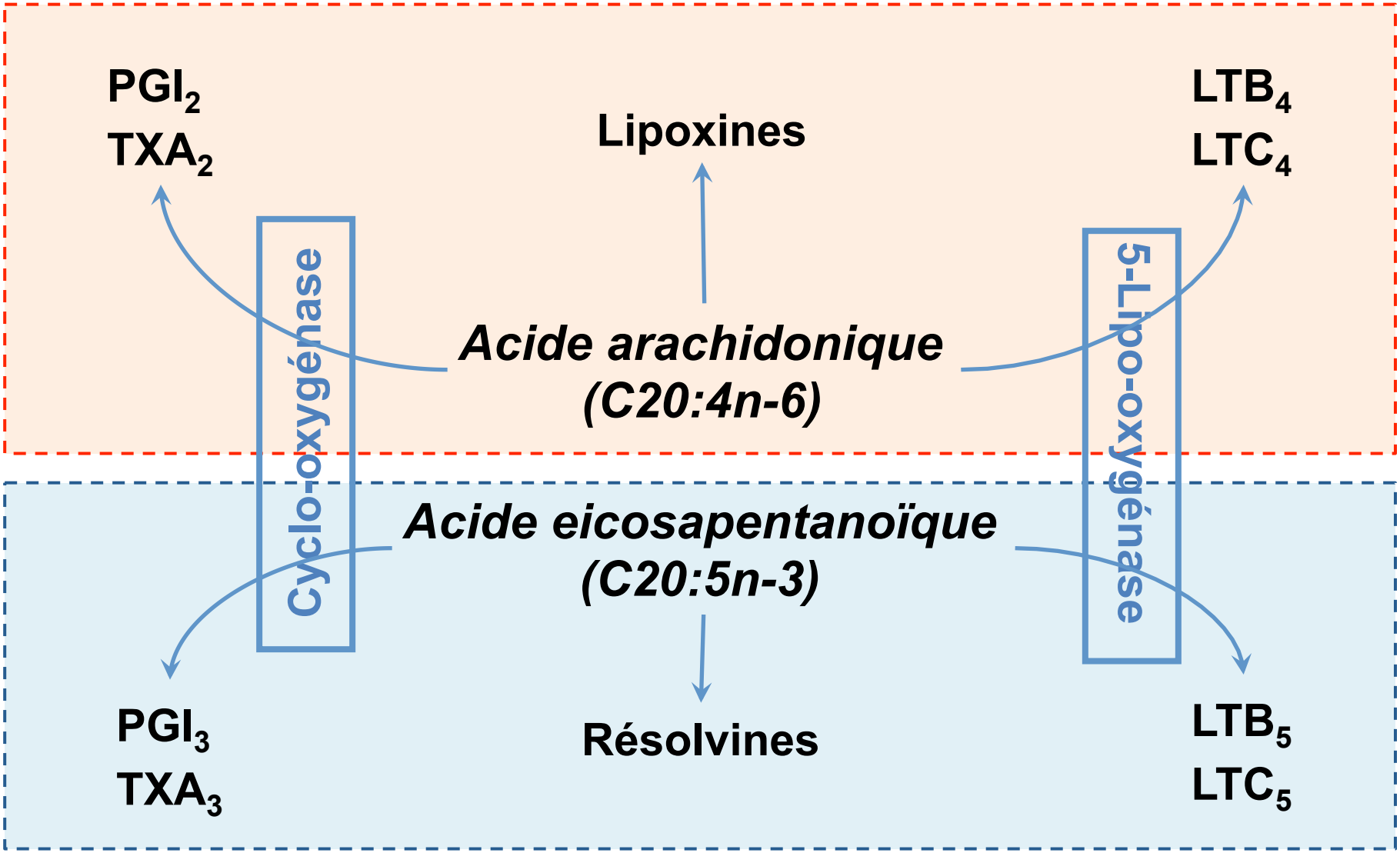
PRO-INFLAMMATOIRE

ANTI-INFLAMMATOIRE

…homo-γ-linolenic acid (20:3n-6) —Δ5-desaturase→ Arachidonic acid (20:4n-6)

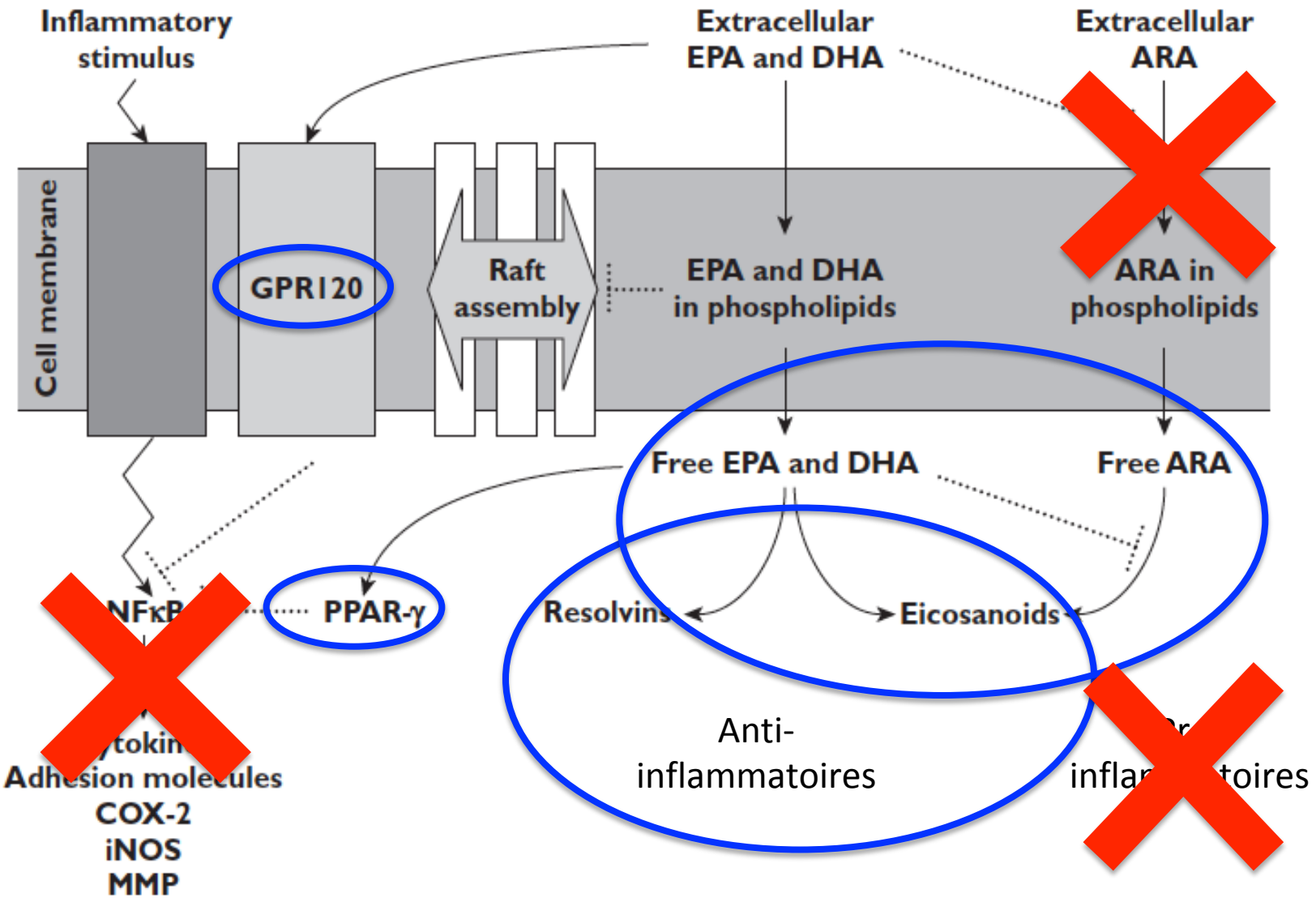
Stearido… —Elongase→ Eicosatetraenoic acid (20:4n-3) —Δ5-desaturase→ Eicosapentaenoic acid (EPA; 20:5n-3) —Elongase, Elongase, Δ6-desaturase, β-oxidation→ Docosahexaenoic acid (DHA; 22:6n-3)

# Médiateurs lipidiques n-6 et n-3

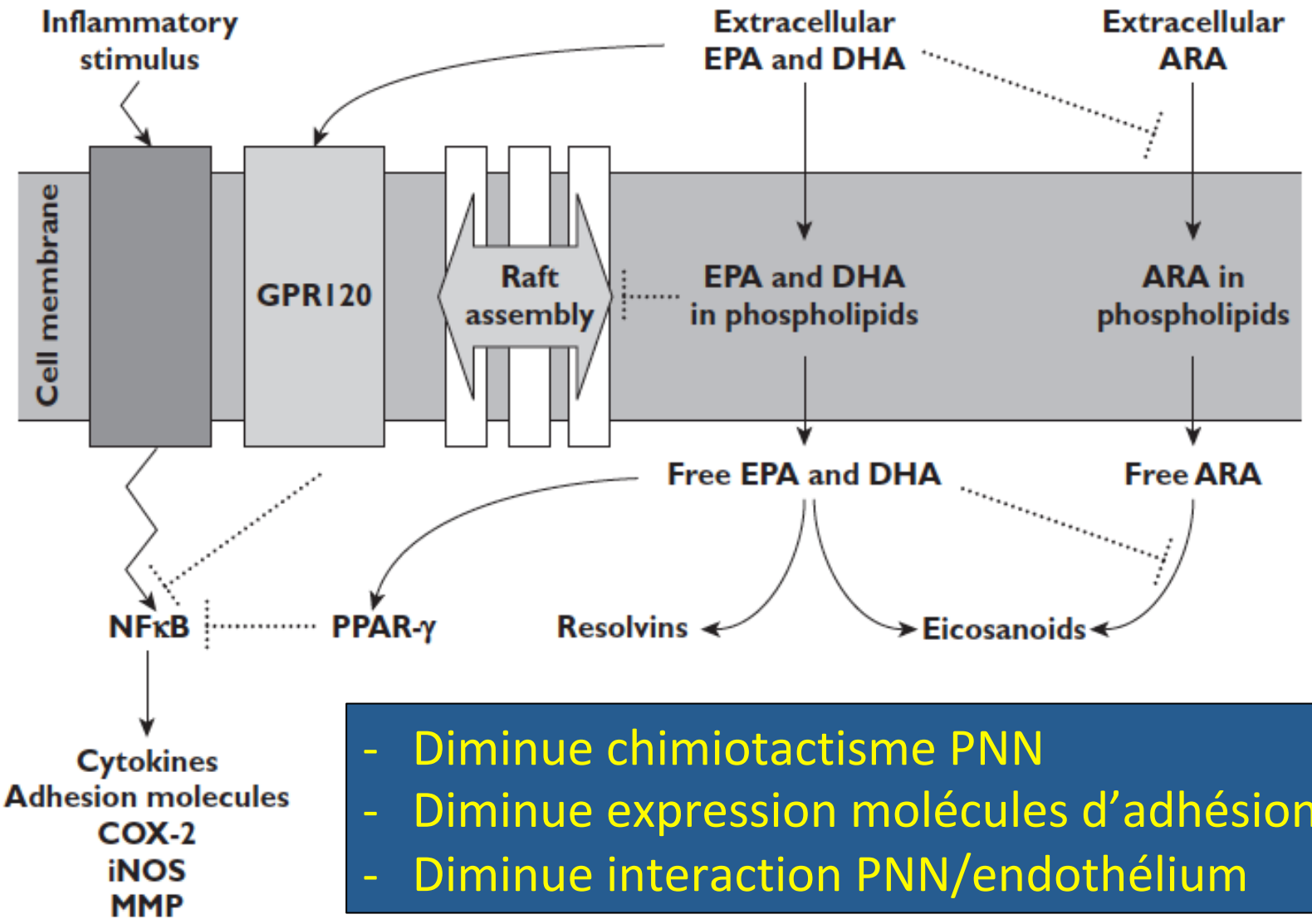



Mayer, Curr Opin Clin Nutr Metab Care 2006;9:140

# Effets anti-inflammatoires des n-3



# Effets anti-inflammatoires des n-3



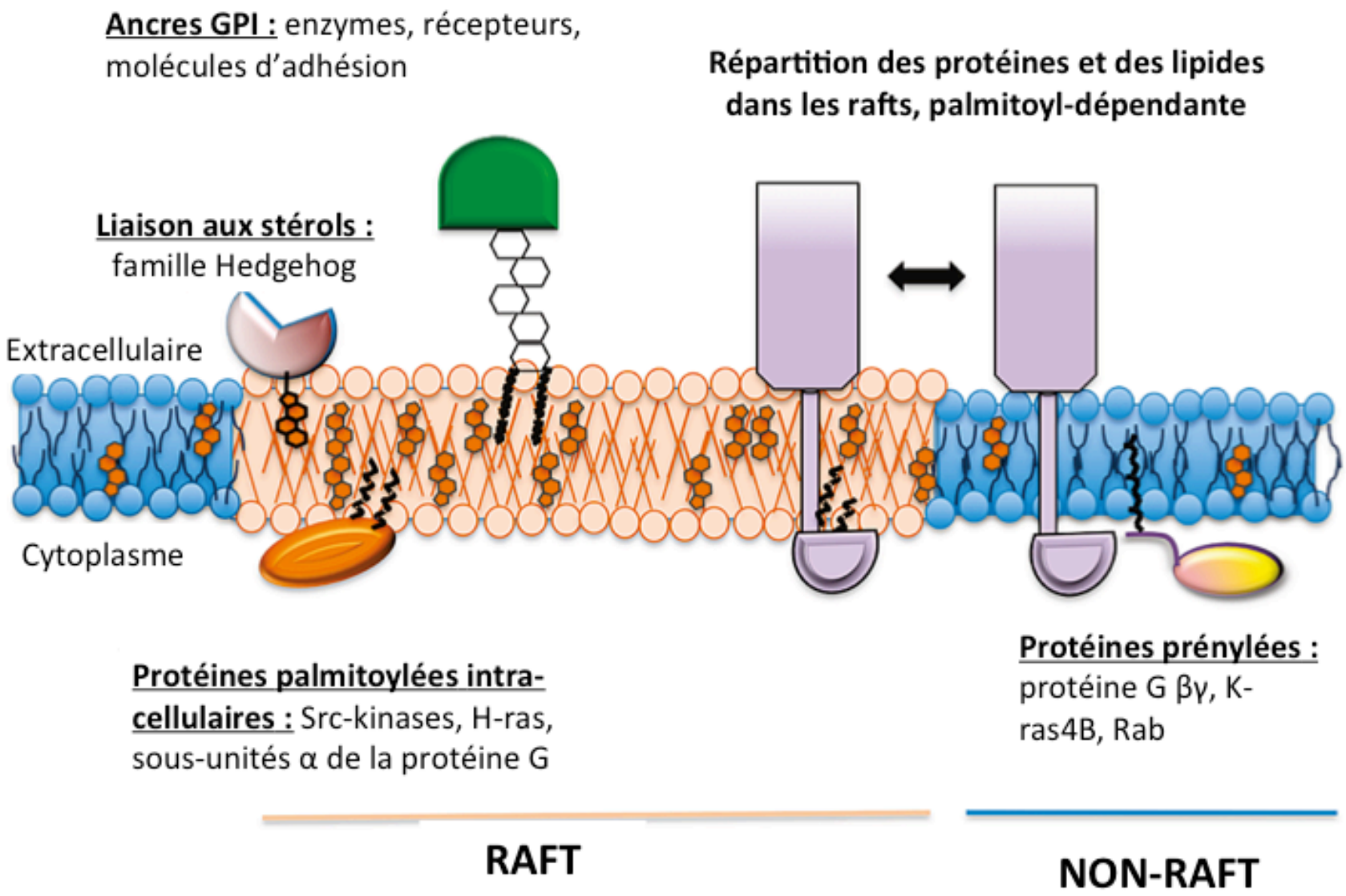

- Diminue chimiotactisme PNN
- Diminue expression molécules d'adhésion
- Diminue interaction PNN/endothélium

# Effets théoriques des TCM

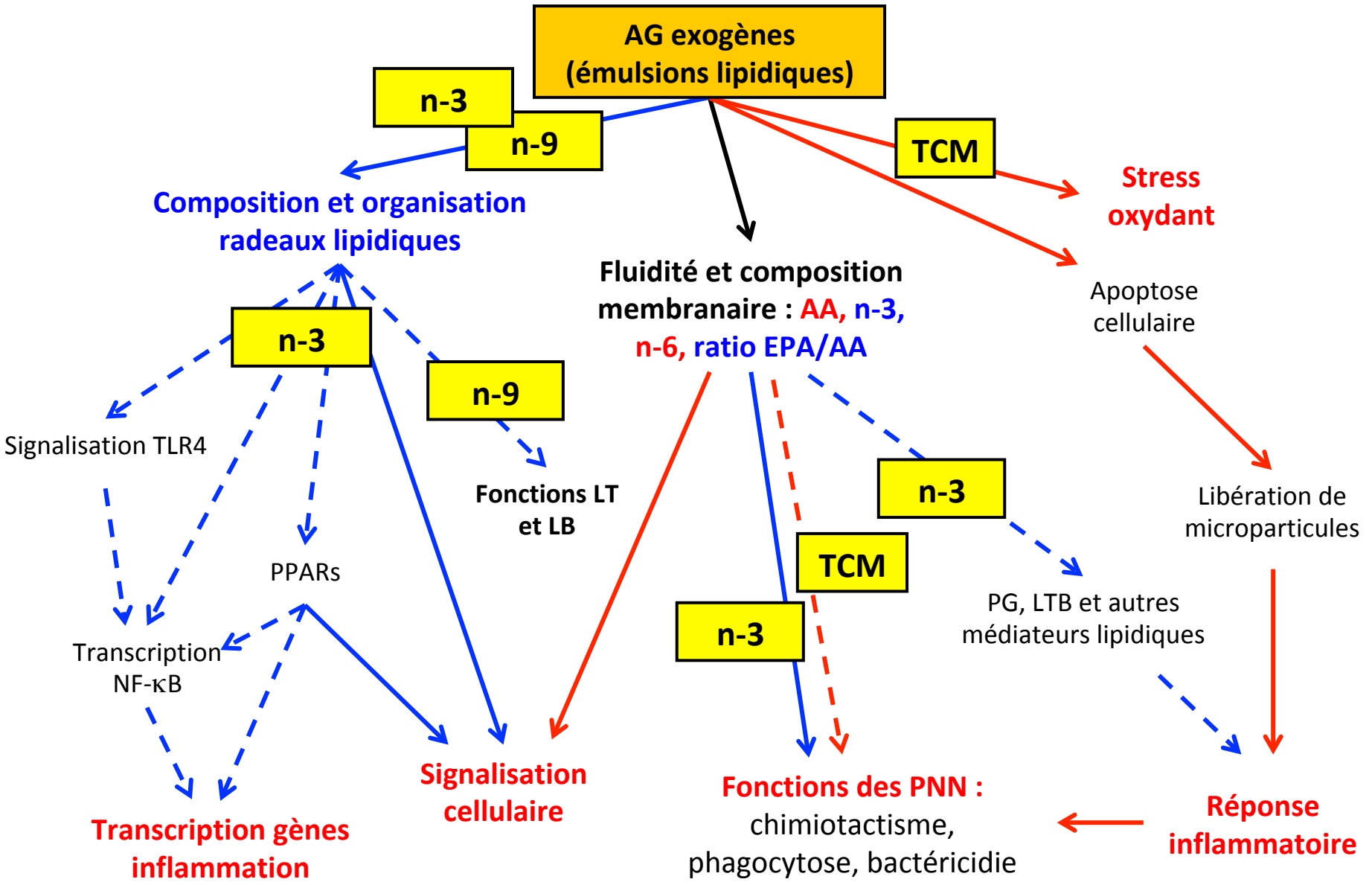
- **« Bénéfiques » (vs. TCL) :**
  - Métabolisme plus rapide
  - Clairance plasmatique rapide
  - Moins de stockage hépatique => moins d'EI

- **« Délétères » :**
  - Activation des PNN + altération fonctions (migration, dégranulation, phagocytose)
  - Production ERO + molécules d'adhésion
  - Rôle pro-inflammatoire du GPR84 ?
    - surexprimé après LPS
    - majore production CK pro-inflammatoires

# Composition des membranes cellulaires



# AG exogènes et inflammation/immunité



# 5) ET EN PRATIQUE ?

# Prescription d'une nutrition parentérale

- Voie centrale dédiée
  - VVP : exceptionnel
- Perfusion continue
- Surveillance :
  - Dextro / 4 h
  - Iono, triglycérides, bilan hépatique

# Prescription d'une nutrition parentérale

- Glucose : 4 g/kg/j = 280-300 g/j
- Acides aminés : 1 g/kg/j = 70 g/j
- Lipides : 0, 7g/kg /j = 50 g/j

# Supplémentation en micronutriments

- Glutamine
- Mélanges polyvitaminiques
- Vitamine K
- Vit B1, B9 et PP
- Mélanges d'oligo-éléments
- Supplémentation spécifique en Zinc et Sélénium (antioxydants)

# Quelle émulsion lipidique ?

- L'émulsion lipidique :
  - À 20 % (100 g / 500 ml)
  - Recommandée en Europe (SFNEP, ESCIM)
  - Proposition de pouvoir « ne pas en utiliser » pour des NP <10 jours chez des patients non dénutris (Canada)

- Pas de critères définitifs de choix entre les différentes émulsions lipidiques

- Contexte clinique ?

# Choc septique

| Study | Number of patients | Duration | Lipid emulsion | Beneficial effects |
|---|---|---|---|---|
| Lindgren [100] | 20 ICU patients with sepsis or multiple injury | 3 days | MCTs/LCTs[4] vs. LCTs[2] | MCTs/LCTs:<br>– Improved nitrogen balance on day 3 |
| Garnacho-Montero [90] | 72 septic patients | 10 days | MCTs/LCTs[5] vs. LCTs[2] | MCTs/LCTs:<br>– Improved nitrogen balance<br>– Improved nutritional markers and catabolic parameters<br>– No effect on mortality<br>– Increased cholestasis enzymes<br>– Increased insulin levels |
| Mayer [104] | 21 septic patients | 5 days | FO[3] vs. LCTs[1] | FO:<br>– Decreased cytokine secretion<br>– No effect on length of mechanical ventilation and mortality |
| Mayer [105] | 10 septic patients | 10 days | FO[3] vs. LCTs[1] | FO:<br>– Predominance of the n−3 acids EPA and DHA acid over AA<br>– Increased anti-inflammatory $LTB_5$<br>– Improved neutrophil function (respiratory burst)<br>– No effect on length of mechanical ventilation and mortality |
| Heller [110] | 661 patients, includi… patients, se… | | …vs. other lipid emulsions | FO: dose-dependent effects<br>– Increased survival<br>– Decreased infection rates, antimicrobial requirements and length of stay |
| Mateu-de… | | >5 days | OO[6] vs. LCTs[2] | OO:<br>– No effect on infection rate, acute-phase proteins, and clinical outcome<br>– Increased blood leucocyte count |
| Friesecke [111] | 166 ICU patients | ≥7 days | MCTs/LCTs[5] + FO[3] vs. MCTs/LCTs[5] | FO:<br>– No effect on inflammation<br>– No effect on clinical outcome |
| Barbosa [19] | 25 septic patients | 5 days | MCTs/LCTs[5] + FO[3] vs. MCTs/LCTs[5] | FO:<br>– No effect on inflammation<br>– No effect on length of mechanical ventilation, ICU stay and mortality<br>– Decreased length of hospital stay |
| Umpierrez [114] | 100 ICU patients | 13 days | OO[6] vs. LCTs[2] | OO:<br>– No effect on blood glucose concentration<br>– No effect on length of stay, mortality, nosocomial infections, and acute renal failure<br>– No effect on inflammatory and oxidative stress markers or in granulocyte and monocyte functions |

Intérêt des omégas 3 et 9 ??

# SDRA

| Study | Number of patients | Duration | Lipid emulsion | Effects |
|---|---|---|---|---|
| Chassard [129] | 6 patients with pancreatitis and ARDS; cross-over study | 8 h | LCTs/MCTs[3] vs. LCTs[2] | MCTs/LCTs: increased oxygen consumption and minute ventilation |
| Planas [126] | Patients with ARDS | | LCTs/MCTs[3] vs. LCTs[1] | MCTs/LCTs: no effect on eicosanoids synthesis |
| Smirniotis [127] | 21 patients with ARDS | 24 h | MCTs/LCTs[4] vs. LCTs[1] | LCTs:<br>— Increased pulmonary venous admixture and mean pulmonary artery pressure<br>— Decreased $PaO_2/FiO_2$<br>MCTs/LCTs: increased oxygen consumption |
| Masclans [132] | 21 patients with ARDS | 12 h | MCTs/LCTs vs. | LCTs:<br>— Increased infusion, cardiac output, oxygen consumption and oxygen delivery increased (all $p < 0.05$)<br>— Pulmonary hemodynamics, arterial oxygen tension, mixed venous partial pressure of oxygen and venous admixture ratio remained unaltered. |
| Smyrniotis [128] | 9 patients with and ARDS | | LCTs[1] | LCTs:<br>— Increased pulmonary venous admixture and mean pulmonary artery pressure<br>— Decreased $PaO_2/FiO_2$<br>MCTs/LCTs: increased oxygen consumption and $CO_2$ production |
| Fa [ | ARDS; cross study | 6 h | MCTs/LCTs[3] vs. LCTs[2] | MCTs/LCTs: increased $PaO_2/FiO_2$, oxygen delivery and cardiac index |
| Lek [131] | 13 patients with ARDS | 1 h | MCTs/LCTs[4] vs. saline | MCTs/LCTs:<br>— Decreased $PaO_2/FiO_2$, respiratory system, and increased pulmonary vascular resistance<br>— Increase in total protein and phospholipid concentrations, phospholipase activities, platelet-activating factor and neutrophils, and surfactant alterations in bronchoalveolar lavage |
| Sabater [141] | 16 patients with ARDS | 12 h | MCTs/LCTs/FO[5] vs. LCTs[1] | MCTs/LCTs/FO: no effect on hemodynamic values and gas exchange parameters |
| Sabater [142] | 16 patients with ARDS | 12 h | MCTs/LCTs/FO[5] vs. LCTs[1] | MCTs/LCTs/FO: decreased pro-inflammatory eicosanoids |

EL délétères ??

# Post opératoire

| Study | Patients | Duration | Lipid emulsion | Effects |
|---|---|---|---|---|
| Dionigi [143] | 15 malnourished patients with advanced gastric or esophageal cancer | 2 weeks preoperatively and 1 week after surgery | LCTs[2] vs. glucose | LCTs:<br>— No effect on nutritional status<br>— No effect on humoral and cellular immune response<br>— Decreased post-operative infectious episodes |
| Monson [144] | 30 malnourished patients with gastrointestinal cancer | 7 days post-surgery | LCTs[2] vs. glucose | LCTs:<br>— Decreased cytotoxicity of IL-2-activated PBMNCs<br>— Significantly impaired NK, activity |
| Morlion [147] | 20 post operative patients | 5 days post-surgery | LCTs[1] / [illegible][1] | LCTs/FO increased $LTB_5/LTB_4$ ratio |
| Wachtler [158] | 40 patients undergoing major intestinal surgery | 5 days post-surgery | [illegible] MCTs/LCTs[4] | MCTs/LCTs/FO:<br>— Increased $LTB_5/LTB_4$ ratio<br>— Decreased pro-inflammatory cytokines<br>— No effect on infection rate, ICU and hospital length stay |
| Roulet [148] | 19 patients [illegible] surgery | [illegible] surgery | LCTs[1]/FO[3] vs. LCTs[1] | LCTs/FO modified the platelet composition and changed some parameters of platelet function |
| Linseisen [155] | [illegible] major surgery | 5 days post-surgery | MCTs/LCTs/FO[5] + α-tocopherol vs. LCTs[2] | MCTs/LCTs/FO + α-tocopherol: normalized α-tocopherol plasma concentrations |
| Weiss [159] | 24 patients with major abdominal surgery | 1 day before and 5 days post-surgery | FO[3] vs. LCTs[1] | FO:<br>— Decreased inflammation<br>— No effect on infection rate, on ICU and hospital length stay, on mortality |
| Schauder [157] | 60 patients | 5 days post-surgery | LCTs[1]/FO[3], LCTs[1] or fat-free nutrition | LCTs/FO:<br>— No effect on distribution and proliferation of lymphocytes<br>— Increased production of inflammatory cytokines |
| Furukawa [145] | 35 patients undergoing surgery for gastrointestinal cancer | 7 days before surgery and 14 days post-surgery | LCTs[2] vs. fat-free parenteral nutrition | LCTs:<br>— No effect on CRP<br>— Increased IL-6 in stressed patients; no effect in unstressed patients<br>— Decreased T cell proliferation in stressed patients; no effect in unstressed patients |

Intérêt des oméga 3 . . . ?

# Post opératoire

| | | | | |
|---|---|---|---|---|
| Köller [153] | 30 patients with major abdominal surgery | 5 days post-surgery | MCTs/LCTs/FO[5] vs. LCTs[2] | MCTs/LCTs/FO increased $LTB_5/LTB_4$ ratio |
| Grau [146] | 72 undernourished patients with laparotomy | | MCTs/LCTs[4] vs. LCTs[2] | MCTs/LCTs:<br>— Decreased incidence of intra<br>— abdominal abscesses; no significant differences in the incidence of other infections.<br>— No effect on mortality, except in patients without cancer (decreased mortality) |
| Antebi [167] | 20 patients undergoing major surgery | ≥5 days | MCTs/LCTs vs. LCTs[1] | MCTs/LCTs/OO/FO improved liver function |
| Heller [151] | 44 patients undergoing major abdominal surgery | 5 days | | LCTs/FO:<br>— Improved liver and pancreas functions<br>— No weight loss |
| Grimm [165] | 33 patients with major [illegible] surgery | | MCTs/LCTs/OO/FO[7] vs. LCTs[1] | MCTs/LCTs/OO/FO:<br>— Increased $LTB_5/LTB_4$ ratio<br>— Decreased hospital length of stay |
| Mertes [175] | | 5 days post-surgery | MCTs/LCTs/OO/FO[7] vs. LCTs[1] | MCTs/LCTs/OO/FO: no effect on laboratory parameters and clinical outcome |
| Wichmann [160] | [illegible] patients undergoing major abdominal surgery | 5 days post-surgery | MCTs/LCTs/FO[5] vs. LCTs[1] | MCTs/LCTs/FO:<br>— Increased anti-inflammatory $LTB_5$<br>— Decreased length of hospital stay |
| Berger [161] | 20 patients with abdominal aortic aneurism surgery | 4 days post-surgery | MCTs/LCTs/FO[5] vs. MCTs/LCTs[4] | MCTs/LCTs/FO: no difference on inflammatory markers and clinical outcome |
| Liang [154] | 42 patients undergoing major abdominal surgery | 7 days post-surgery | LCTs/FO[3] vs. LCTs[2] | LCTs/FO:<br>— Decreased inflammatory response<br>— Decreased hospital stay length<br>— No effect on mortality and infectious complications |
| Piper [166] | 44 postoperative patients | 5 days post-surgery | MCTs/LCTs/OO/FO[7] vs. LCTs[2] | MCTs/LCTs/OO/FO improved liver function |
| Badia-Tahull [176] | 27 patients undergoing gastrointestinal surgery | 5 days post-surgery | OO[6] vs. FO[3]/OO[6] | FO:<br>— Reduced infection incidence<br>— No effect on inflammatory and nutritional markers |

Intérêt des oméga 3 … ?

# Post opératoire

| Study | Patients | Duration | Lipid emulsion | Effects |
|---|---|---|---|---|
| Jiang [152] | 206 patients undergoing gastrointestinal cancer surgery | 7 days post-surgery | LCTs[2]/FO[3] vs. LCTs[2] | LCTs/FO:<br>— Decreased SIRS<br>— Decreased hospital length stay |
| Hallay [168] | 26 patients undergoing major abdominal surgery | 5 days post-surgery | MCTs/LCTs/OO/FO[7] vs. MCTs/LCTs[4] | Hepatic effect of the intravenous lipid emulsions did not differ significantly between the two emulsions |
| Makay [156] | 26 patients undergoing gastric cancer surgery | 1 day before and 5 days post-surgery | LCTs/FO[3] vs. LCTs[1] | LCTs/FO: no effect on biochemical parameters, complications, or length of hospital stay or mortality. |
| Ma [169] | 40 postsurgical gastrointestinal tumor patients | 5 days post-surgery | vs. MCTs/LCTs[4] | MCTs/LCTs/OO/FO:<br>— Decreased postoperative LDL<br>— No effect on metabolic parameters, proinflammatory cytokine levels, adverse events, and clinical outcomes |
| De Miranda Torrinhas [177] | 63 gastr… | …erative | FO[3] vs. MCTs/LCTs[1] | FO:<br>— Increased anti-inflammatory cytokines<br>— Decreased leukocyte oxidative burst, maintained monocyte percentage expressing HLA-DR and CD32, and increased CD32 neutrophil expression<br>— No changes in post-operative infections, length of ICU and hospital stay. |
| Ma [170] | 99 patients undergoing gastrointestinal cancer surgery | 1 day before and 7 days post-surgery | MCTs/LCTs/FO[5] vs. MCTs/LCTs[4] | FO:<br>— No effect on metabolic parameters, proinflammatory cytokine levels, adverse events, and clinical outcomes<br>— Improved lipid metabolism |

Intérêt des oméga 3 … ?

# Les points clés

- … la dénutrition tue !

- Nutrition parentérale = 2ème intention

- Controverse persistante sur le choix des EL :
  - Discordance expérimental / clinique
  - Faibles effectifs
  - Comparaisons difficiles : bcp d'EL différentes
  - Nécessité de RCT

# Conclusions


- Un potentiel théorique...
  - Anti-inflammatoire
  - Anti-pro-oxydant
  - Modulateur de l'immunité

- Les questions en suspens :
  - Le bon mélange ? N-3 / n-9 ? nouveaux TG de synthèse ?
  - Le timing (modulation de l'immunité : SIRS/CARS) ?


VITAMINES
A
D
B1
C