Conversions et compétitions entre acides gras essentiels chez l'animal et l'homme

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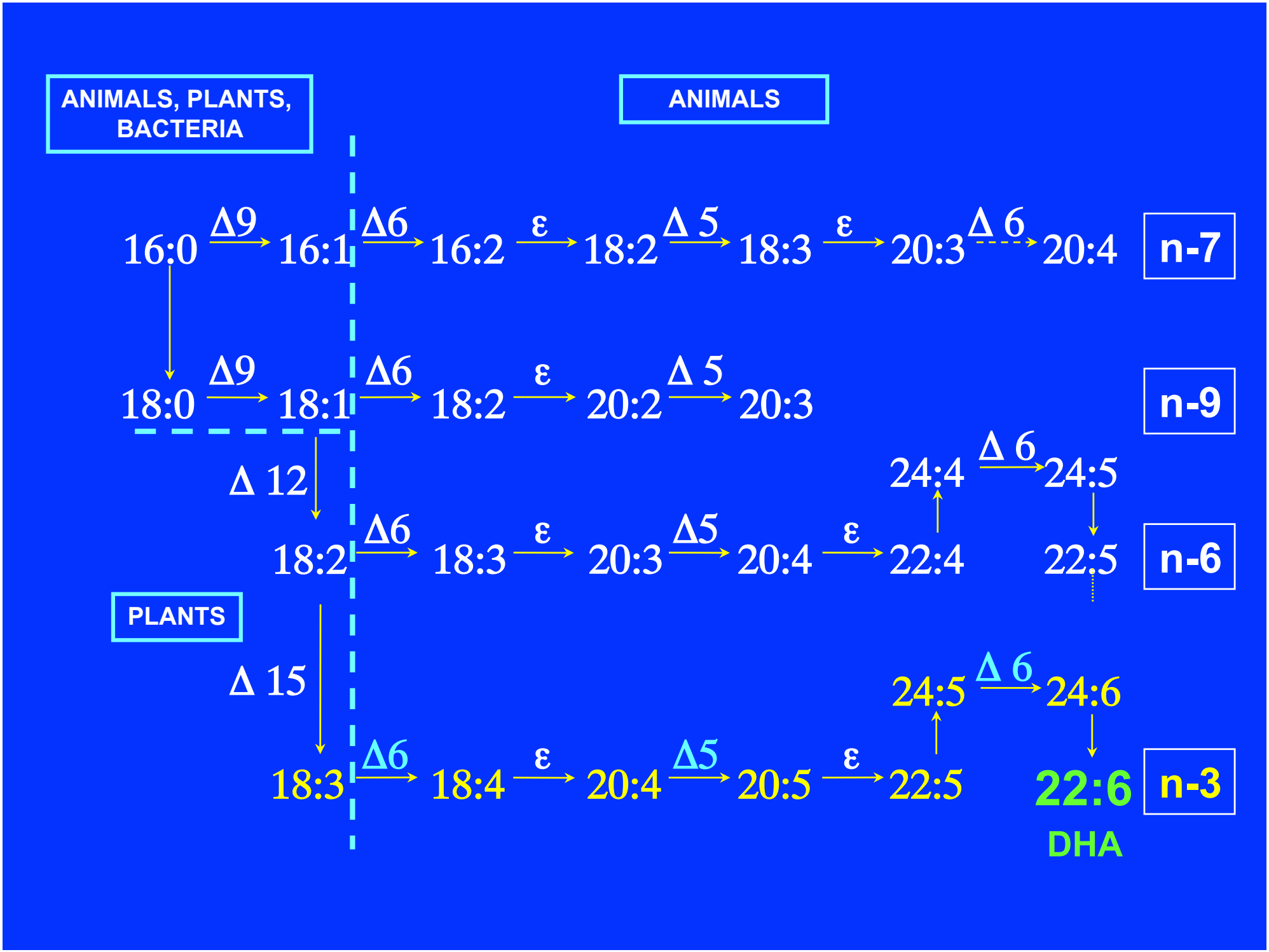
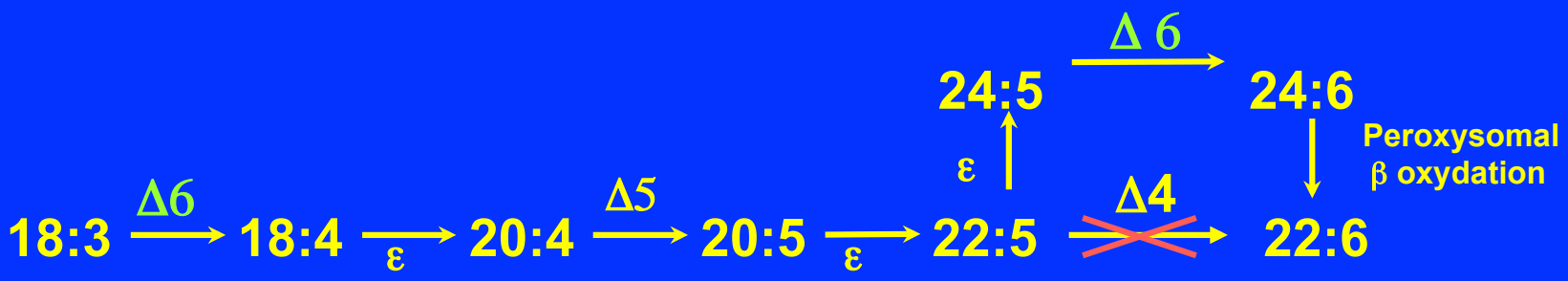
- The pathway
- Genetical aspects
- Δ6 desaturase (FADS2) acts at different places
- Régulation of Δ6 et Δ5 desaturases by fatty acids
- Limits of DHA biosynthesis


ANIMALS, PLANTS, BACTERIA
ANIMALS
16:0 Δ9 16:1 Δ6 16:2 ε 18:2 Δ 5 18:3 ε 20:3 Δ 6 20:4
n-7
18:0 Δ9 18:1 Δ6 18:2 ε 20:2 Δ 5 20:3
n-9
Δ 12
24:4 Δ 6 24:5
18:2 Δ6 18:3 ε 20:3 Δ5 20:4 ε 22:4 22:5
n-6
PLANTS
Δ 15
24:5 Δ 6 24:6
18:3 Δ6 18:4 ε 20:4 Δ5 20:5 ε 22:5 22:6
DHA
n-3

''Sprecher'' pathway



Voss et al., 1991

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Δ6 and Δ5 desaturases

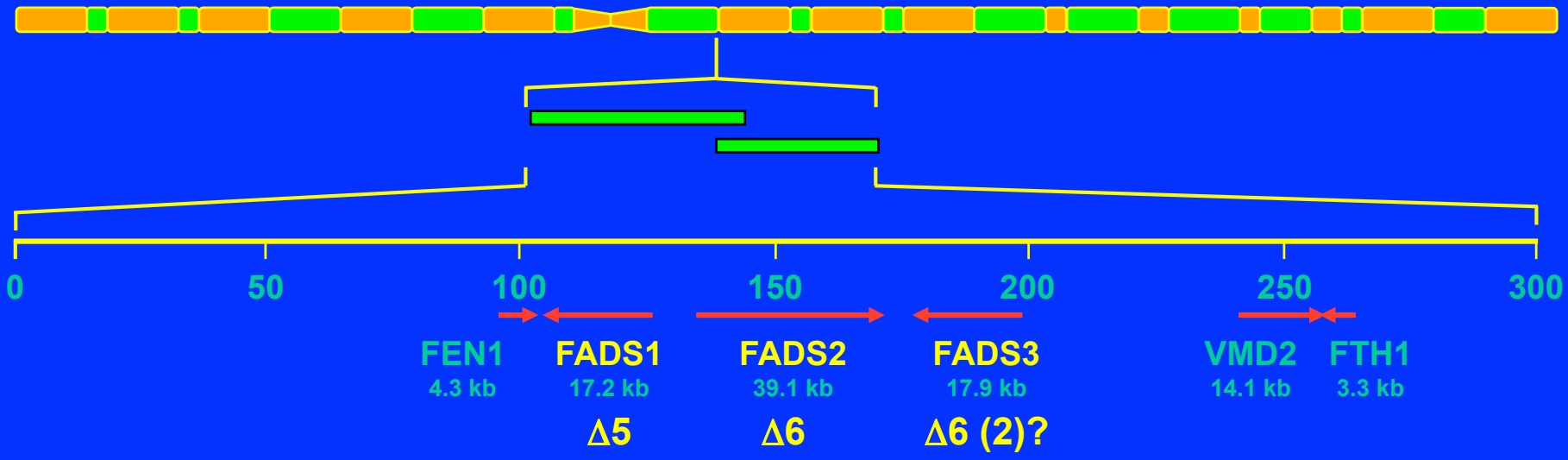
Cloning and sequencing :

- **Δ6 mouse and human** *(Cho et al., 1999a)*
- **Δ6 rat** *(Aki et al., 1999)*
- **Δ5 human** *(Cho et al., 1999b; Leonard et al., 2000)*

Existence of a second ''human Δ6 isoform'' (70 % homology)
(EMBL, Li et al., not published)

Second rat ''Δ6 isoform'' cloned and sequenced
(EMBL, D'Andréa et al., not published)

Confirmation of 3 genes FADS1, FADS2, FADS3 on chromosome 11 in human
(Marquardt et al., 2000)



NB : **Δ6 et Δ5 désaturases contain a cytochrome b5 domain**

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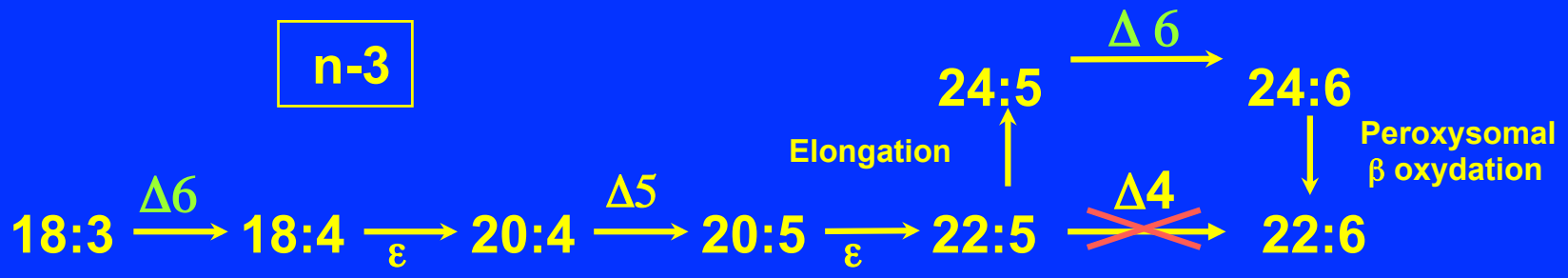
''Sprecher'' pathway

Voss et al., 1991



Δ6 DESATURASE

ONE OR TWO

Competitions between substrates
(Geiger et al., 1993)
Déficiences in human fibroblasts
(Williand et al., 2001)

Certain cells do not synthesize C22:6 n-3 although they have an active Δ6 desaturase
(Marzo et al., 1996; Chen et al., 1993)

Démonstration that the cloned Δ6 is active on both C 18:3 n-3 et le C 24:5 n-3
(D'Andréa et al., 2002)

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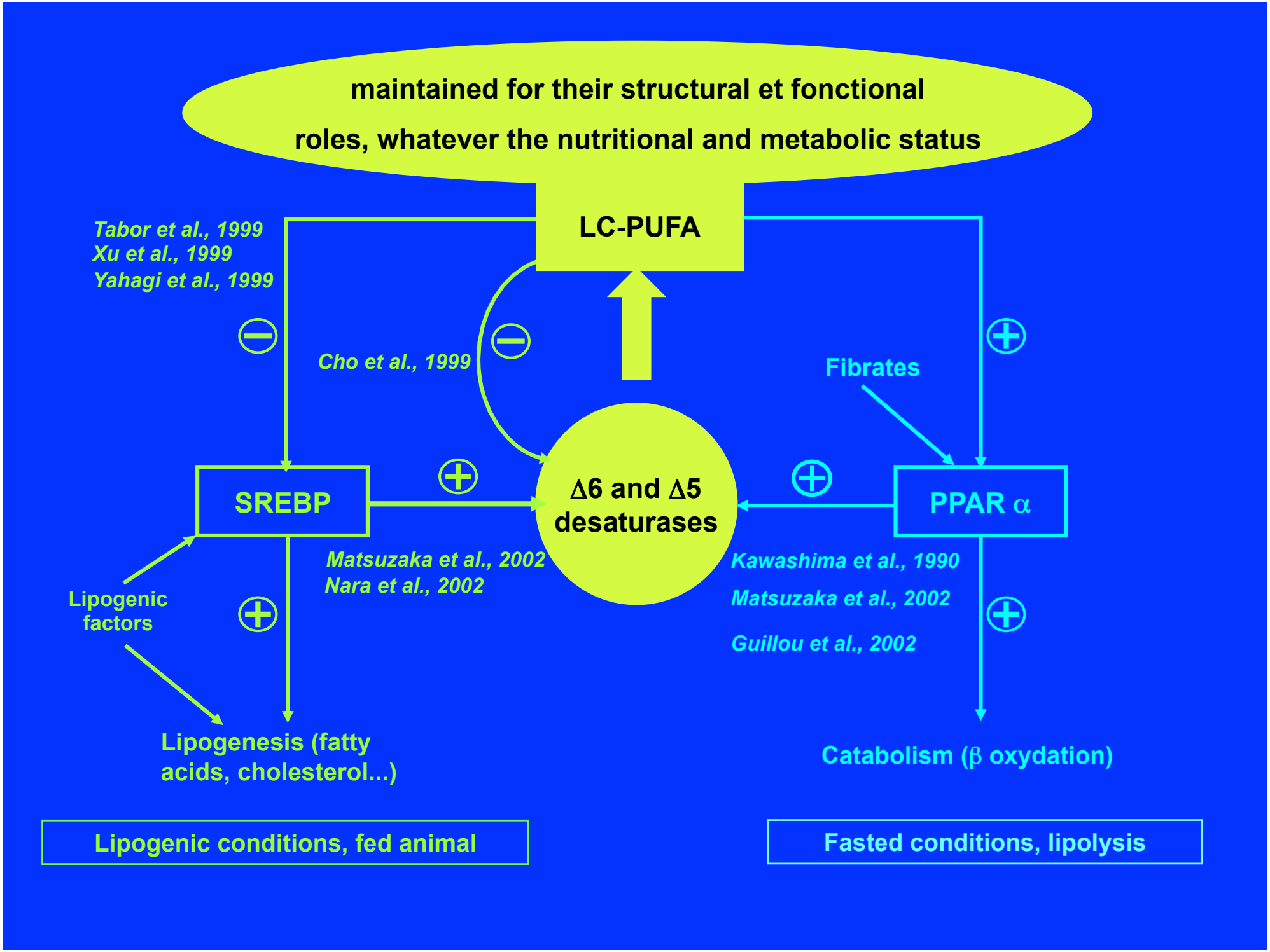
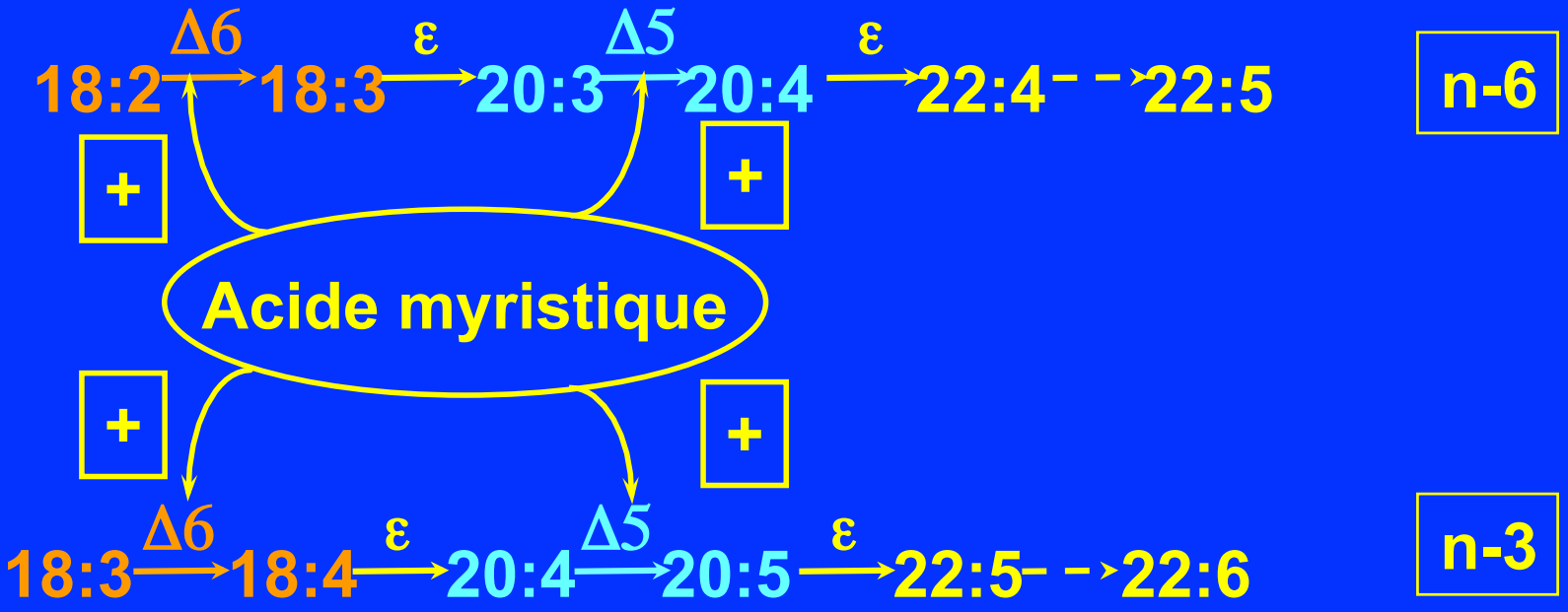
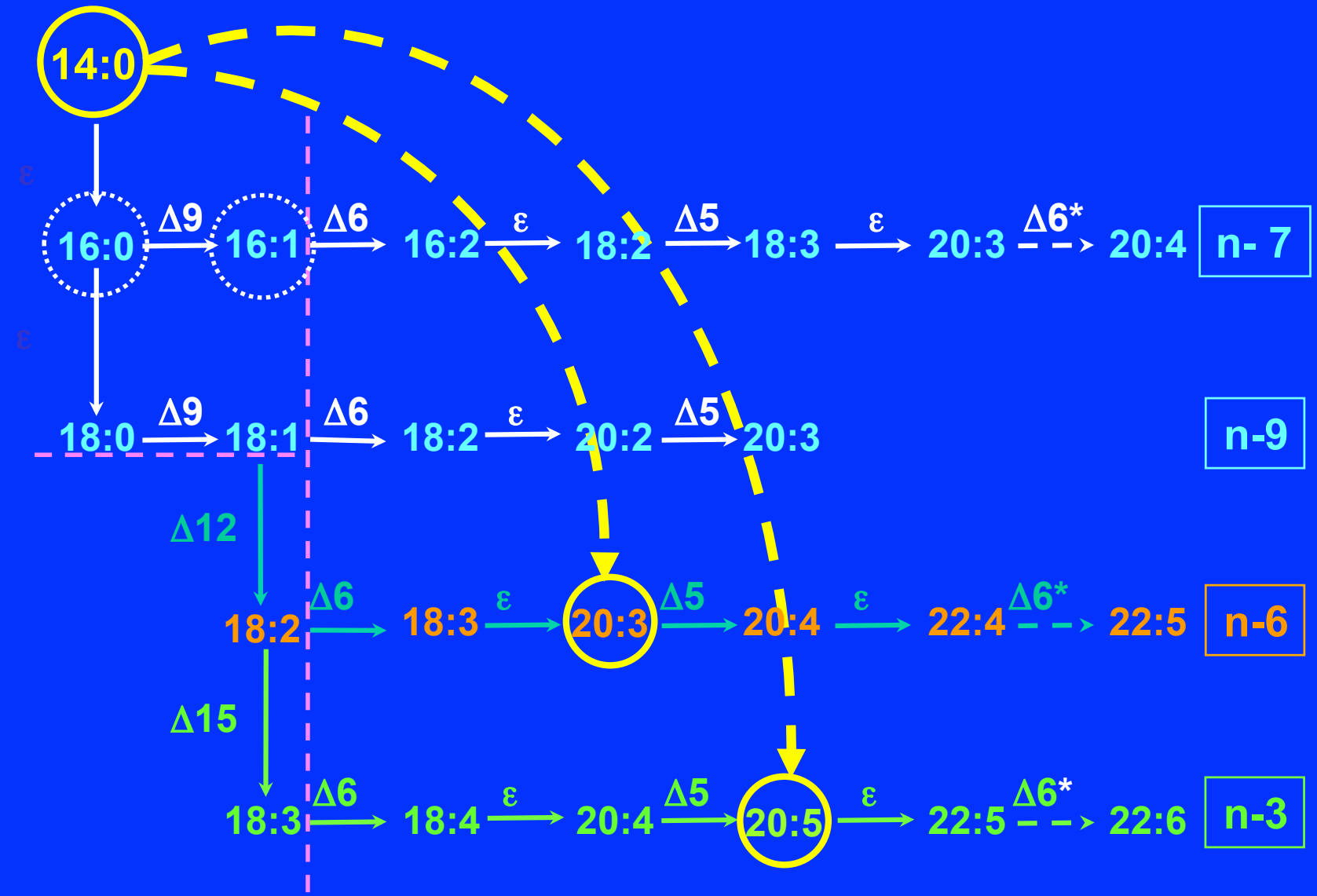

maintained for their structural et fonctional
roles, whatever the nutritional and metabolic status
LC-PUFA
Tabor et al., 1999
Xu et al., 1999
Yahagi et al., 1999
Cho et al., 1999
Fibrates
SREBP
Δ6 and Δ5
desaturases
PPAR α
Matsuzaka et al., 2002
Nara et al., 2002
Kawashima et al., 1990
Matsuzaka et al., 2002
Guillou et al., 2002
Lipogenic
factors
Lipogenesis (fatty
acids, cholesterol...)
Catabolism (β oxydation)
Lipogenic conditions, fed animal
Fasted conditions, lipolysis

Rôle de l'acide myristique sur le métabolisme des acides gras polyinsaturés



- Expression génique ?
- Modification co ou post traductionnelle ?
- Autres ?

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



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

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Limits of DHA biosynthesis

- Low activity of the pathway
- Doses and sources of C 18:3 n-3
- Activity of Δ6 desaturase
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- Activity of elongases
- Peroxysomal β-oxydation
- Retroconversion
- Competitions with the n-6 family
- Tissu specificity

CONVERSION

C 18:3 n-3 ⟶ C 22:6 n-3

- 10 fois moins active chez l'homme que chez le rat
  (Descomps, 2003)
- Organisme entier : conversion < 5 %, probablement < 1%
  (*(Brenna, 2002; Cunnane, 2001; Crawford,2004)*
- Le DHA plasmatique inhibe la conversion DPA → DHA *(Pawloski et al., 2004)*
- Meilleure conversion chez la femme que l'homme
  (Burdge et al., 2002)
- Etude avec des traceurs : controverses

	Pawlosky et al., 2001	Goyens et al., 2005
18:3 n-3 ➔ 20:5 n-3 :	0.2 %	7 %
20:5 n-3 ➔ 22:5 n-3 :	63 %	1% (des 7%)
22:5 n-3 ➔ 22:6 n-3 :	23 %	

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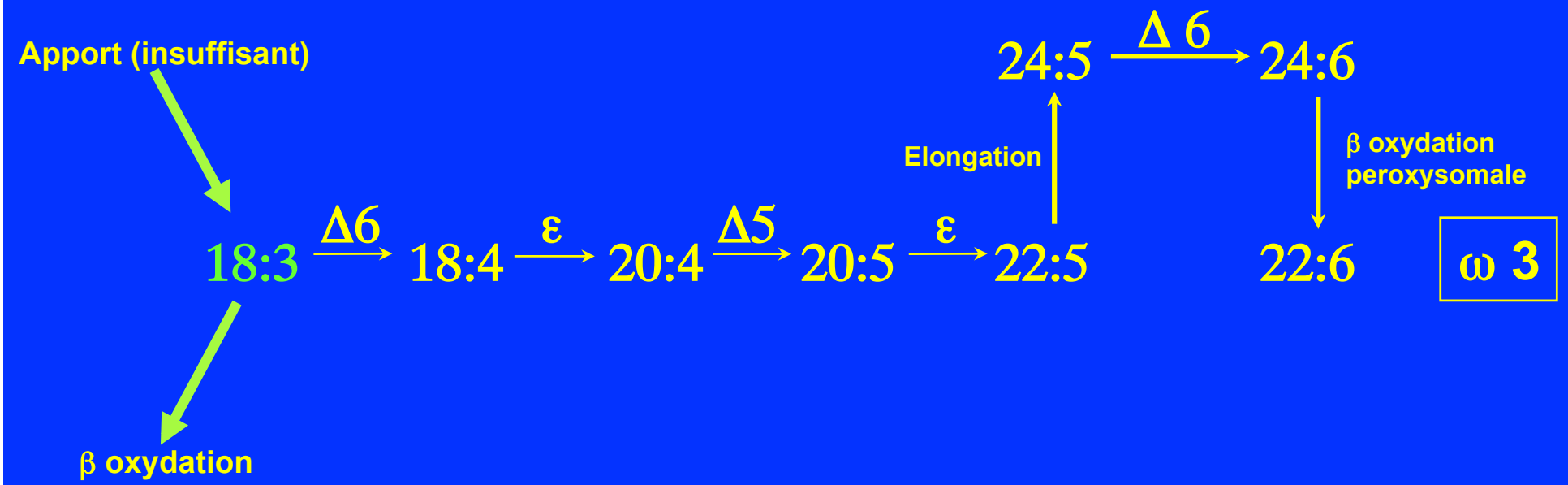
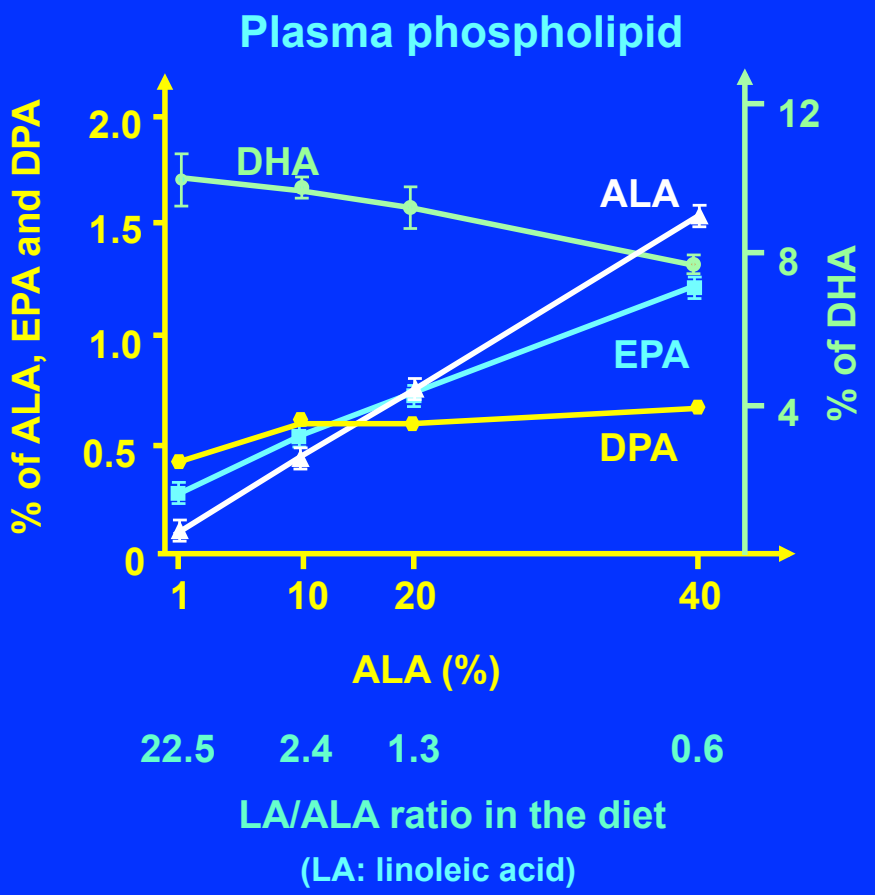
Disponibilité du substrat

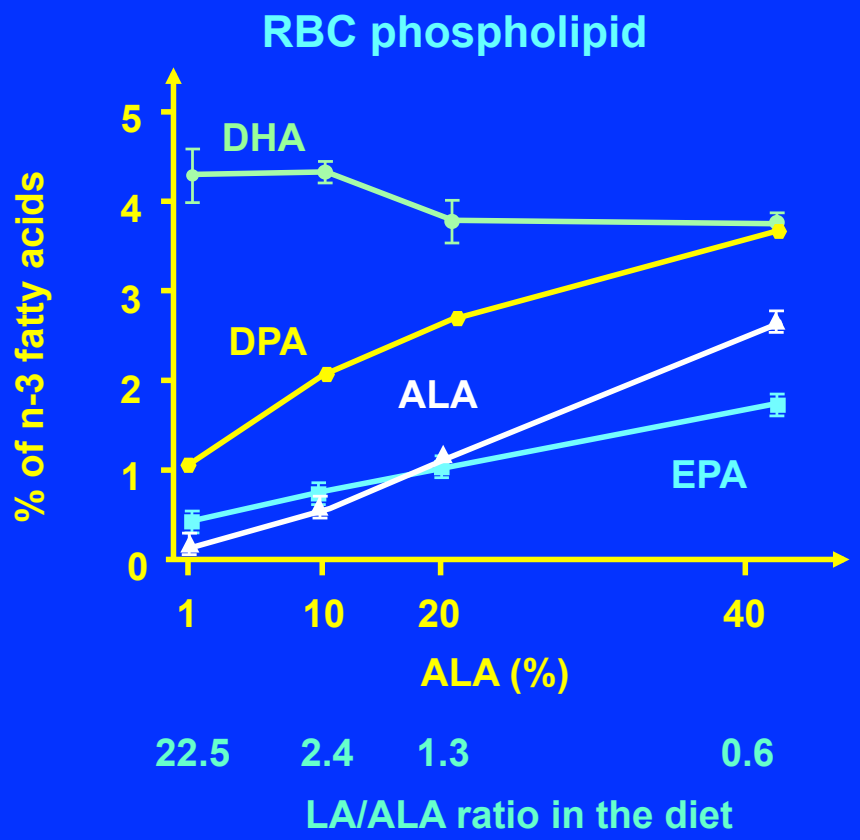


60 % en CO_2, 30 % en acétate

(Brenna, 2002; Cunnane, 2001)

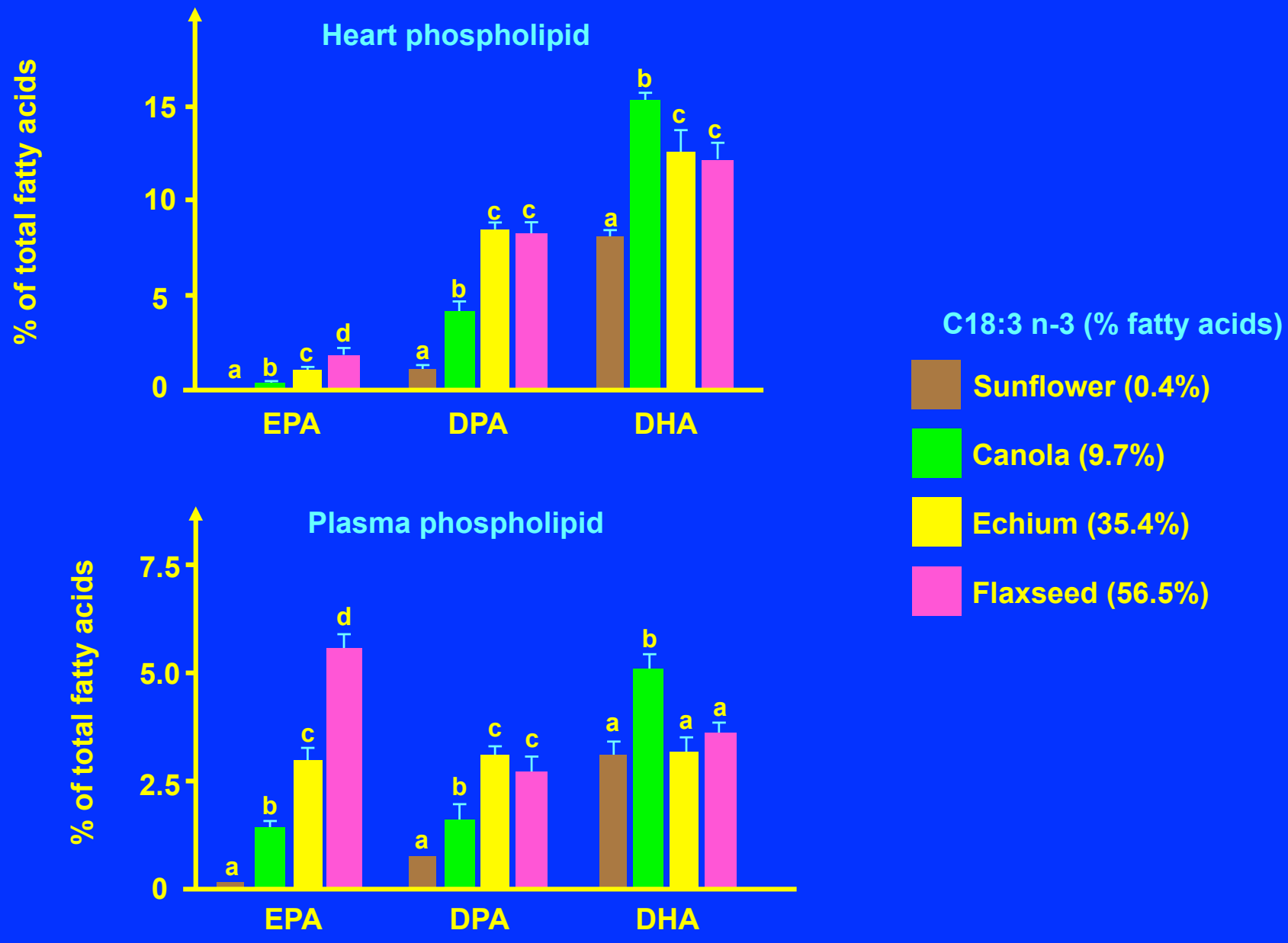
Effet dose de l'acide α-linolénique (ALA) sur sa conversion en dérivés





Morise et al., 2004

Importance des doses d'acide α-linolénique sur la disponibilité du DHA



Cleland et al., 2005

Acides gras des lipides du sérum des volontaires
(% des acides gras totaux)

Acide gras	Régime "contrôle"		Régime "Lin"
C 16:0	19.5 ± 1.8	*	18.5 ± 1.7
C 18:0	5.9 ± 0.9		5.7 ± 0.8
C 18:1 n-9	22.6 ± 2.0		23.3 ± 2.4
C 18:2 n-6	31.3 ± 3.6		31.6 ± 4.2
C 18:2 cis 9 trans 11	0.28 ± 0.07	**	0.42 ±0.13
C 18:3 n-3	0.44 ± 0.11	**	0.93 ± 0.30
C 20:4 n-6	7.7 ± 1.1		6.6 ± 1.1
C 20:5 n-3	0.52 ± 0.22	**	0.80 ± 0.17
C 22:5 n-3	0.35 ± 0.08	**	0.45 ± 0.10
C 22:6 n-3	1.51 ± 0.24	*	1.67 ± 0.29
C 18:2 n-6 / C 18:3 n-3	71 ± 23	**	34 ± 12
Σ n-6 / Σ n-3	14.3 ± 2.5	**	10.2 ± 1.8

C 18:3 n-3 (% acides gras)	1.0	2.75

Weill et al., 2002

moyennes ± SD. Différences significatives: * $p < 0.05$; ** $p < 0.01$

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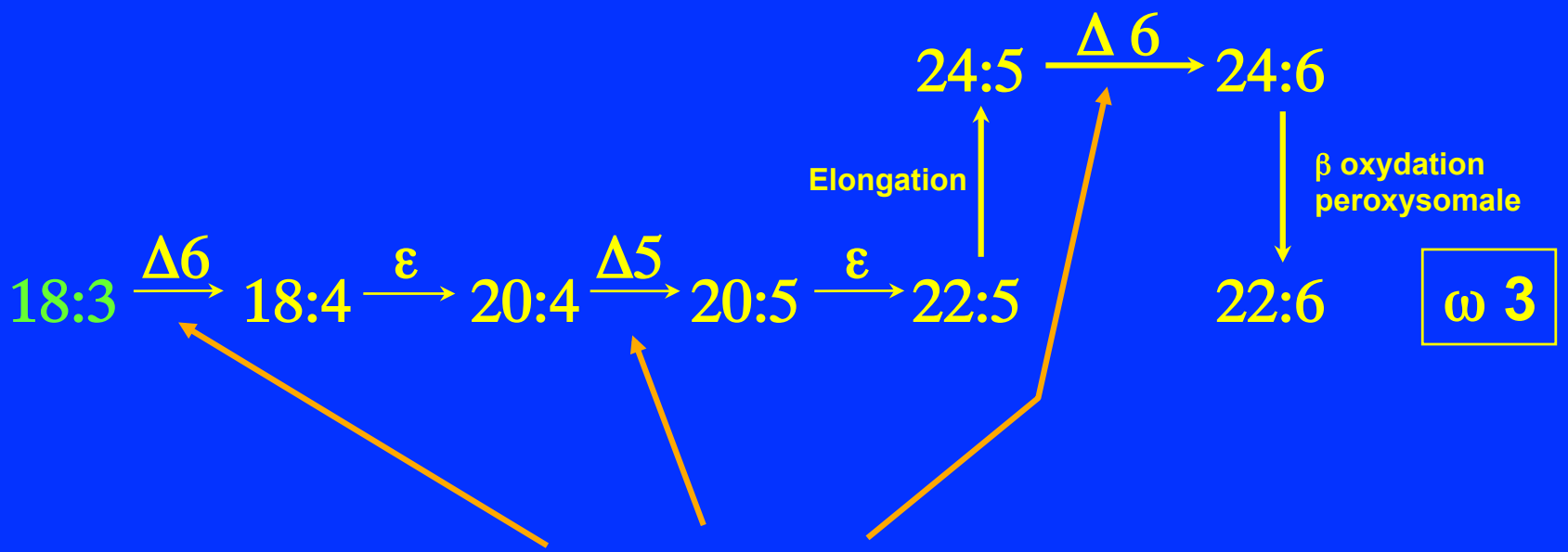
Voie faiblement active



Activités :

- Faibles
- Variables (situations physiologiques et physiopathologiques)
- Synthèse limitée du DHA

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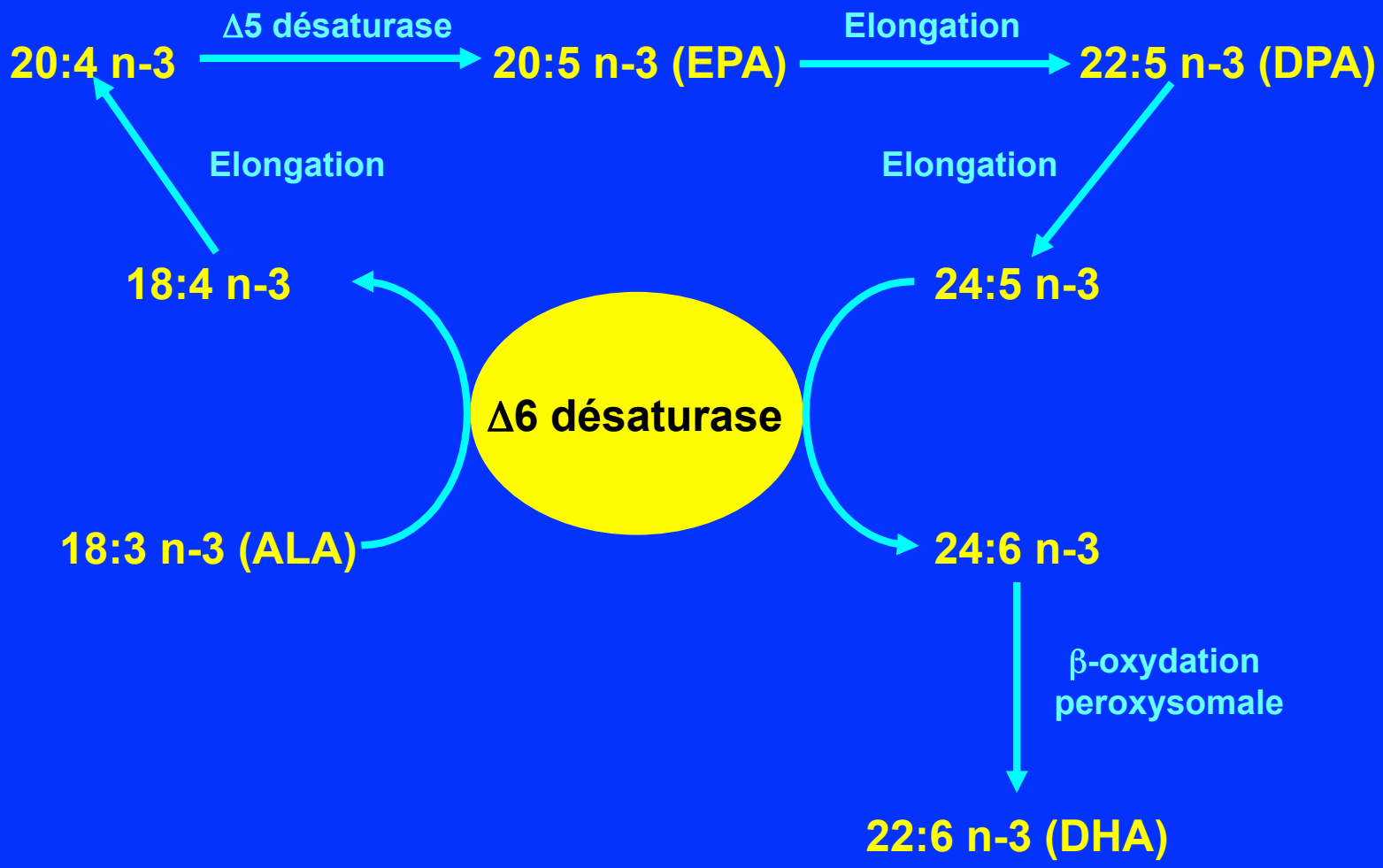
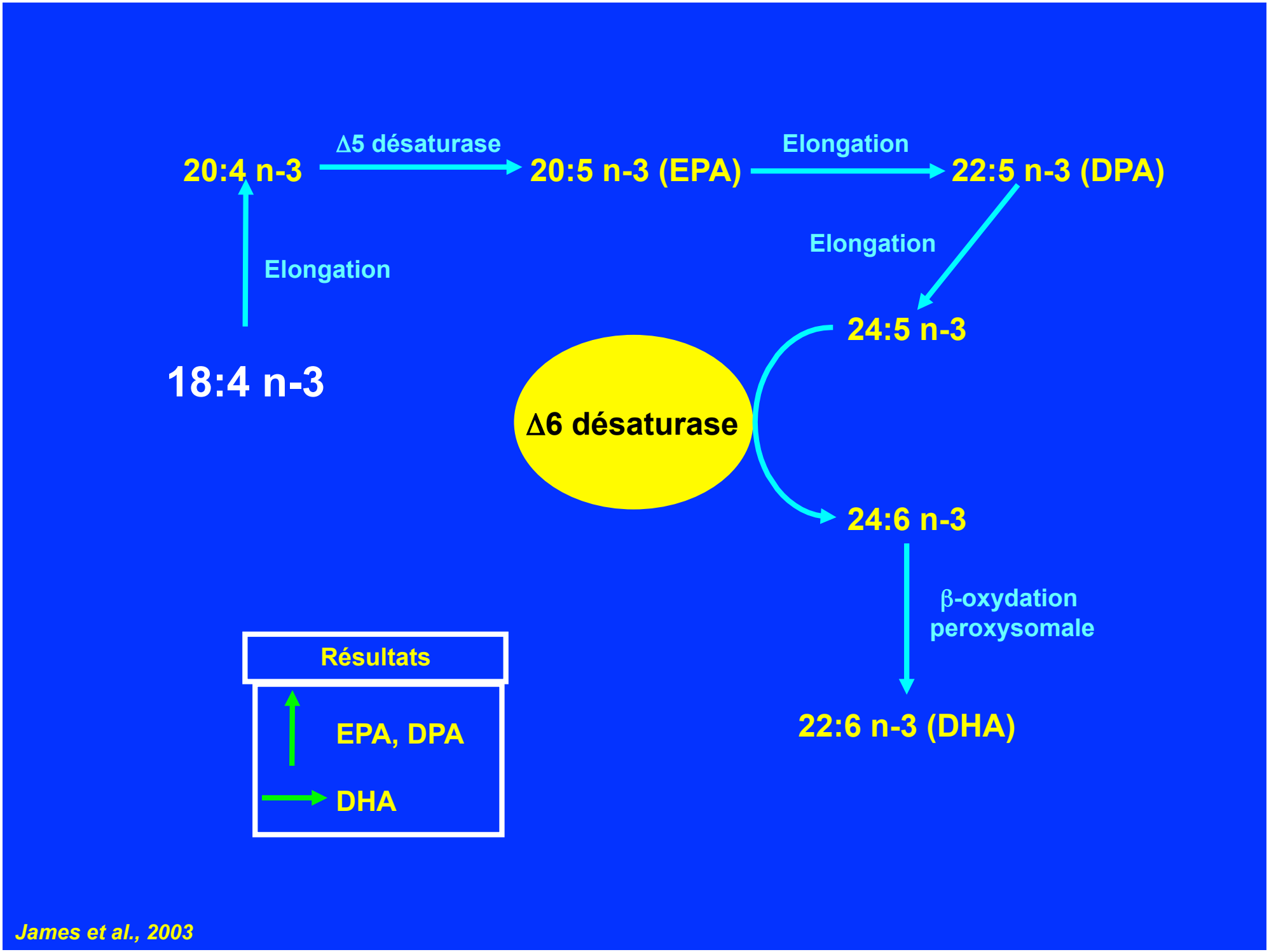


L'acide α-linolénique (ALA) est à la fois précurseur et compétiteur pour la synthèse du DHA



James et al., 2003

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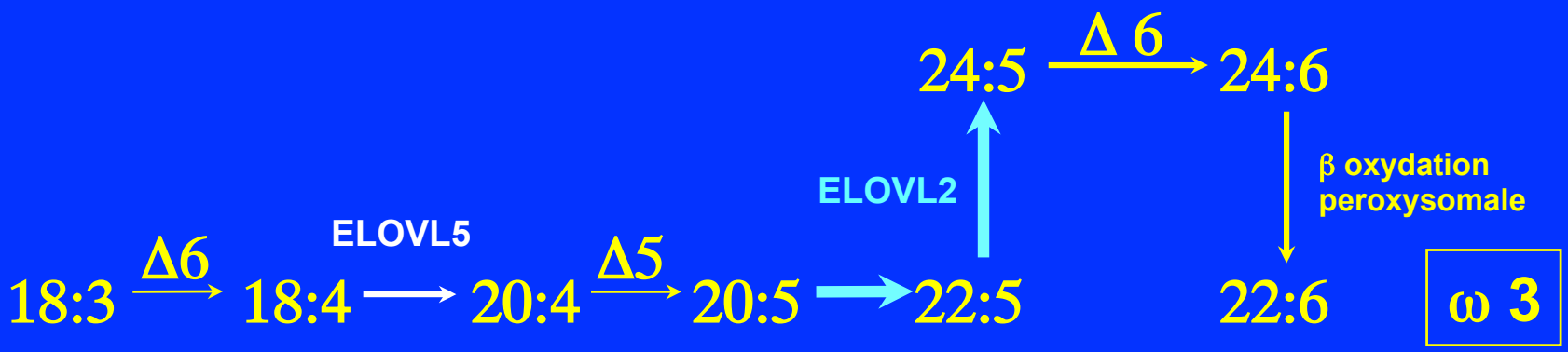
Activité des élongases



ELOVL2 (human) : plus active pour 20→22 que 22→24

Leonard et al., 2002

NB : - Etape 20:5 → 22:5 lente d'après Goyens et al., 2005

- Pas d'accumulation de 24:5 ni de 24:6

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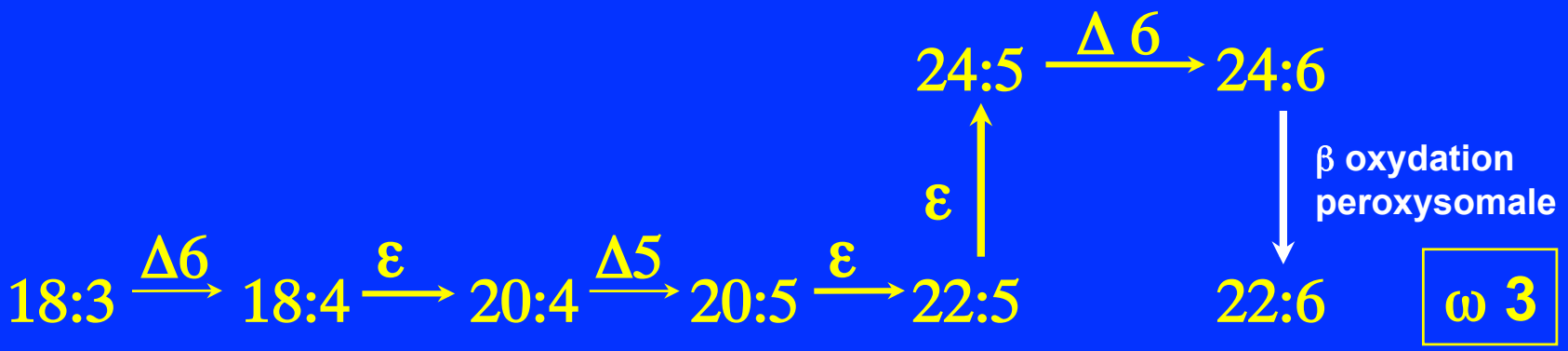
β-oxydation peroxysomale



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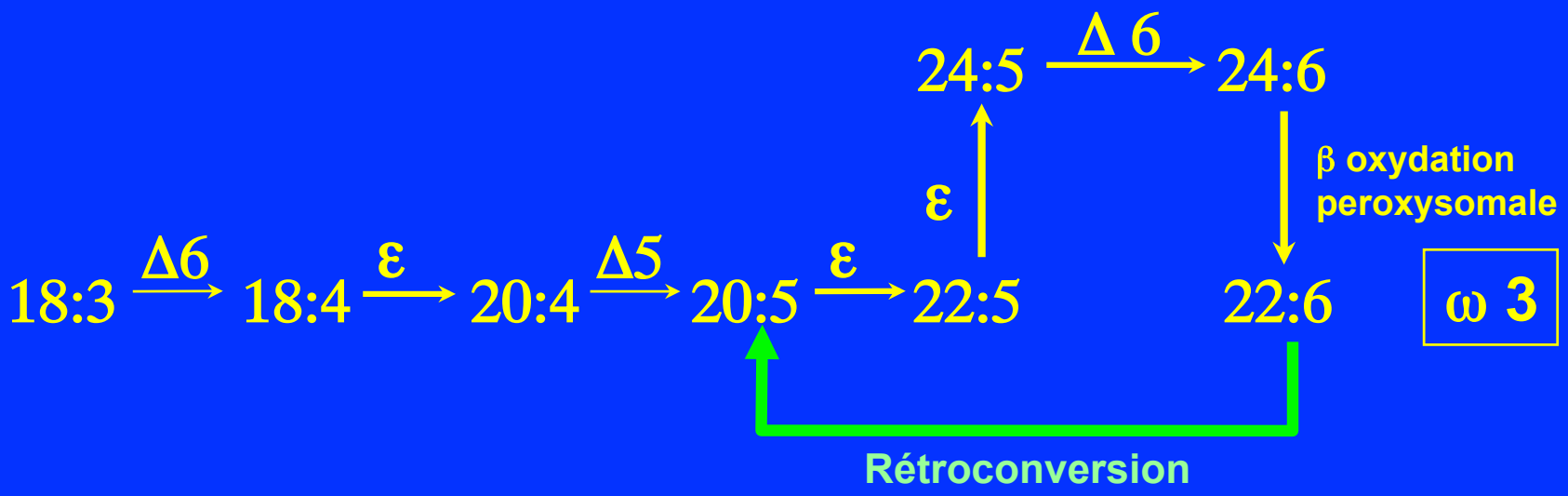
Rétroconversion du DHA



- Processus peroxysomal (étape de β–oxydation + enoyl réductase) (Schlenk et al., 1969; Gronn et al., 1991)
- Existe pour la famille n-6 (22:5 → 20:4) (Phyllis et al., 2000)
- Activité faible (1.4% chez l'homme, Brossard et al., 1996)
- Plus forte si déficit en C20:5 n-3 (9%, Conquer et al., 1997)
- Assurer le niveau de C20:5 pour la production des prostaglandines

⇒ Probablement mineure si apport suffisant en C18:3 n-3

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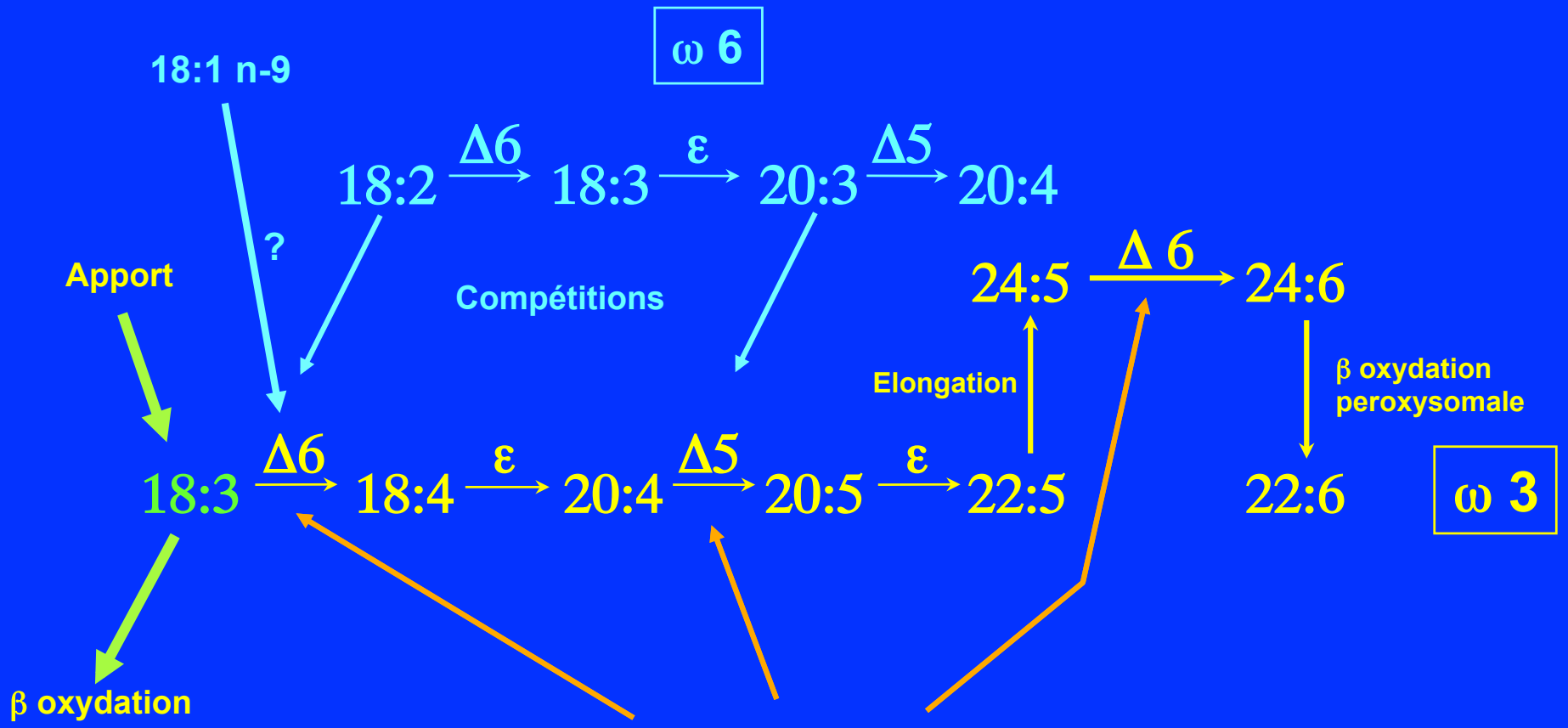
- Competitions with the n-6 family….. and oleic acid
- Tissu specificity



Activités :

- **Faibles**
- **Variables (situations physiologiques et physiopathologiques)**
- **Synthèse limitée du DHA**

➔ **Situations nutritionnelles : excès de n-6, oléique, (trans ?)**

COMPETITION AVEC LES n-6

ENFANT

Méta-analyse ***(Clark et al., 1992)*** **:**

Par rapport à l'allaitement maternel :

- **Déficit de conversion de 50 % quand 18:2 n-6 / 18:3 n-3 > 20**
- **Déficit de conversion de 27 % quand 18:2 n-6 / 18:3 n-3 = 5**

ADULTE

- **Réduction de conversion**
  (Mantzioris et al., 1994; O'Dea et al., 1988)
- **50 % de réduction quand 18:2 n-6 passe de 15 à 30 g / jour**
  (Emken et al.,1994)
- **Conversion inversement corrélée à la quantité de C18:2 n-6**
  (Gibson et al., 2004, Hussein et al., 2005, Lands 2005)

is the role of the ratio linoleic / linolenic major or minor ?

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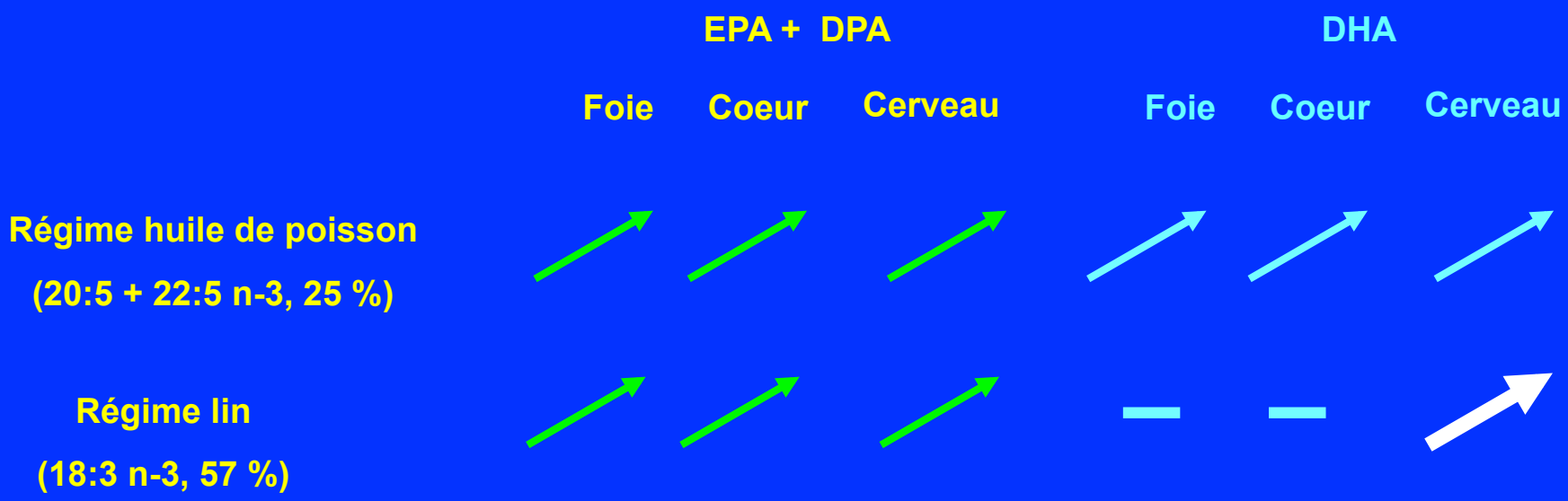
La conversion C18:3 n-3 → C22:6 n-3 serait tissu spécifique



Suggère une conversion désaturation spécifique du cerveau

(Barcelo-Coblijn et al., 2005)

Δ6 et Δ5 exprimées dans le cerveau (*Cho et al., 1999*)

Synthèse du DHA dans les astrocytes (*Bernoud et al., 2001*)

Synthèse dans les neurones (*Spector dans Barcelo-Coblijn et al., 2005)*

EFFECT OF DIETARY n-3 PUFA DEPRIVATION IN THE RAT:

DHA synthesis from α-linolenic acid by rat brain is unaffected by dietary n-3 deprivation. (15 weeks, 14C α-linolenic acid)

(Igarashi et al., 2007)

Dietary n-3 PUFA deprivation for 15 weeks upregulates elongases and desaturase expression in rat liver but not brain

(Igarashi et al., 2007)

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