Structured phospholipids, as proposed vehicles of DHA and Neuroprotectin D1.

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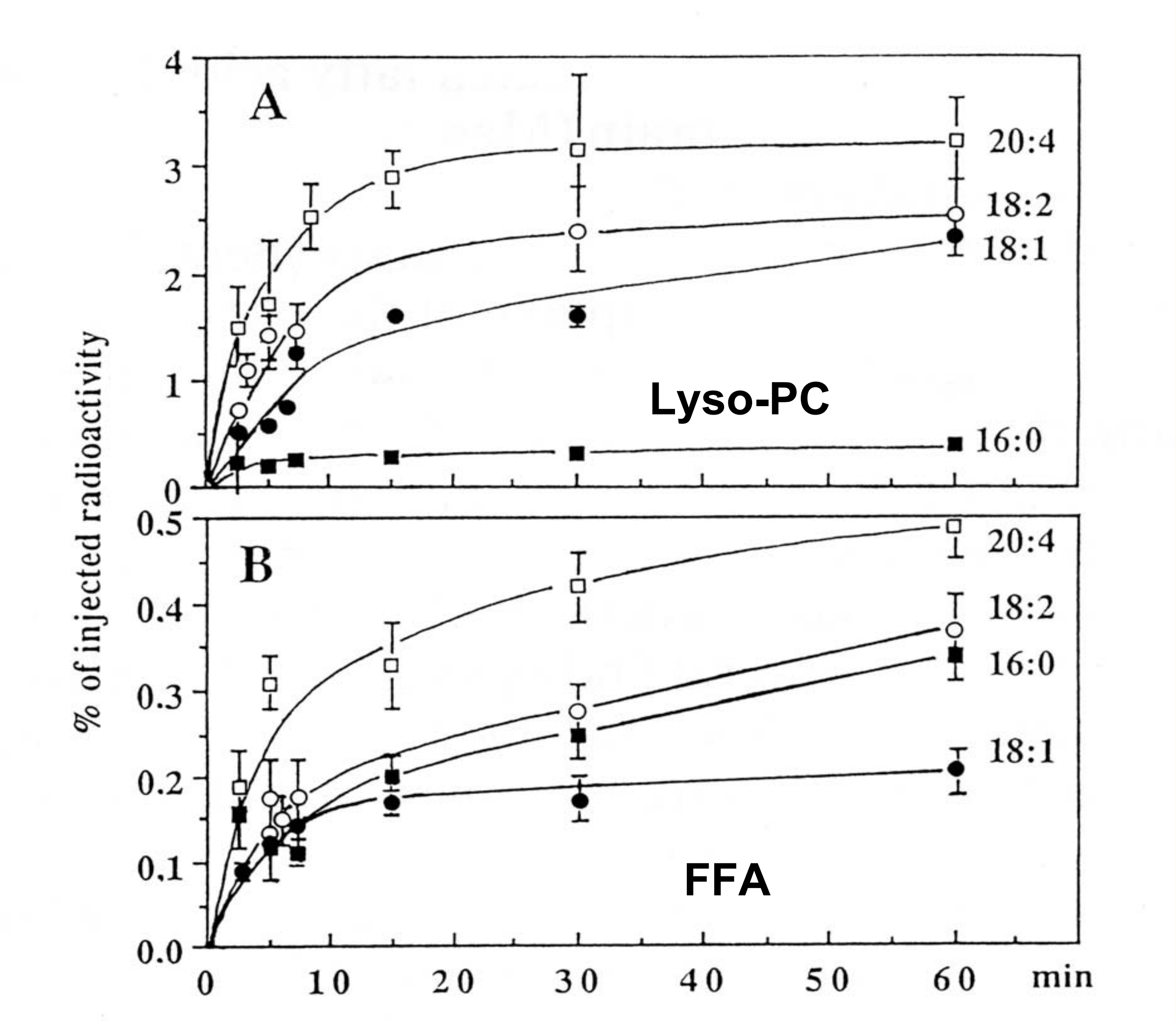
Background & approach

It has been assumed that unesterified fatty acids cross the blood brain barrier. They are then provided by circulating albumin, which also transports LysoPLs.

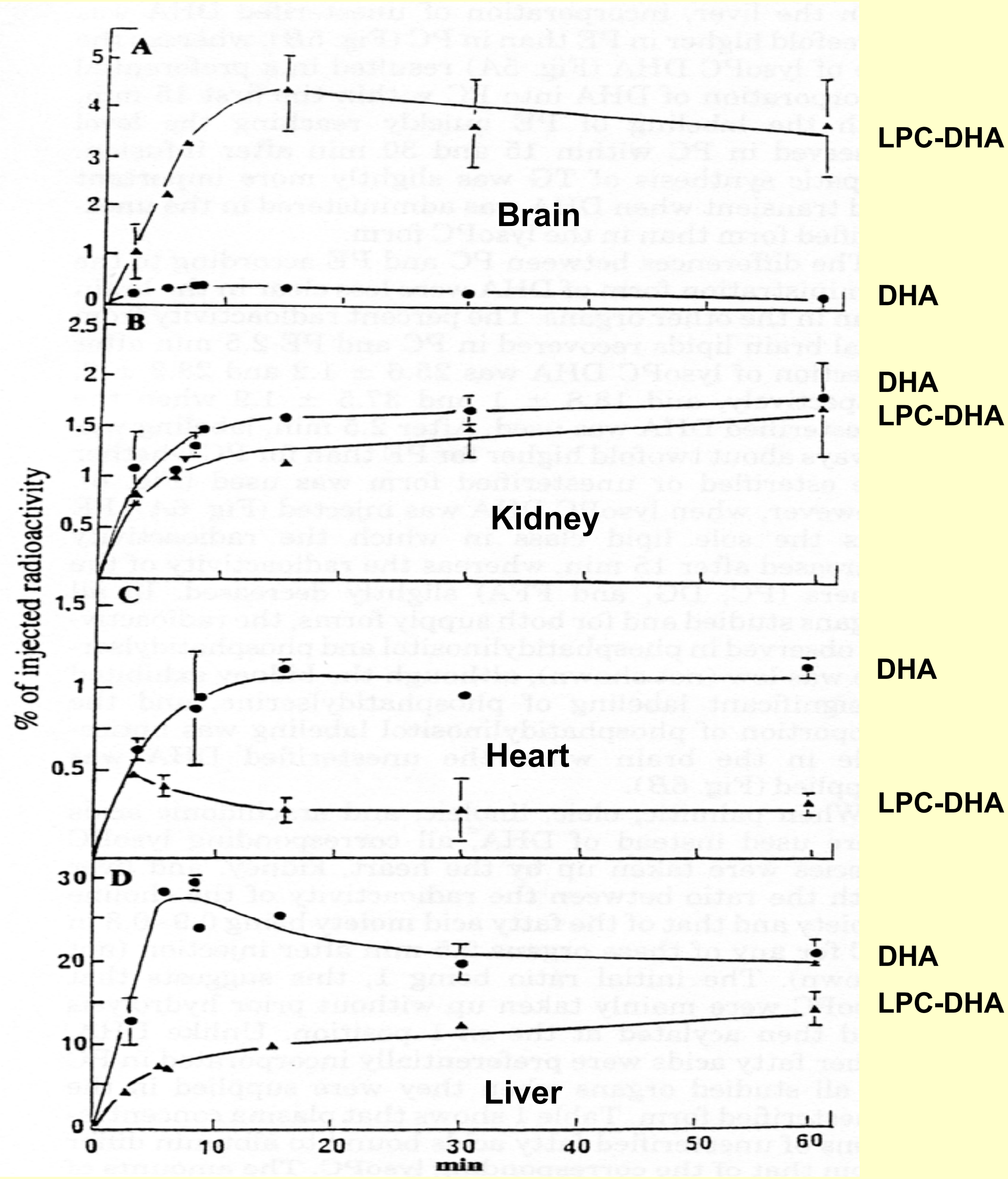
Fatty acids, in particular DHA, either in their unesterified form or esterified at the sn-2 position of LysoPC, were compared for their brain accretion or incorporation into red blood cell phospholipids as an index of brain accretion.

^{14}C-labeled species were used when injected to the rat or ^{13}C-labeled ones when ingested by rats or humans.

Uptake of FA by the brain



Thiès et al J. Neurochem. 1992



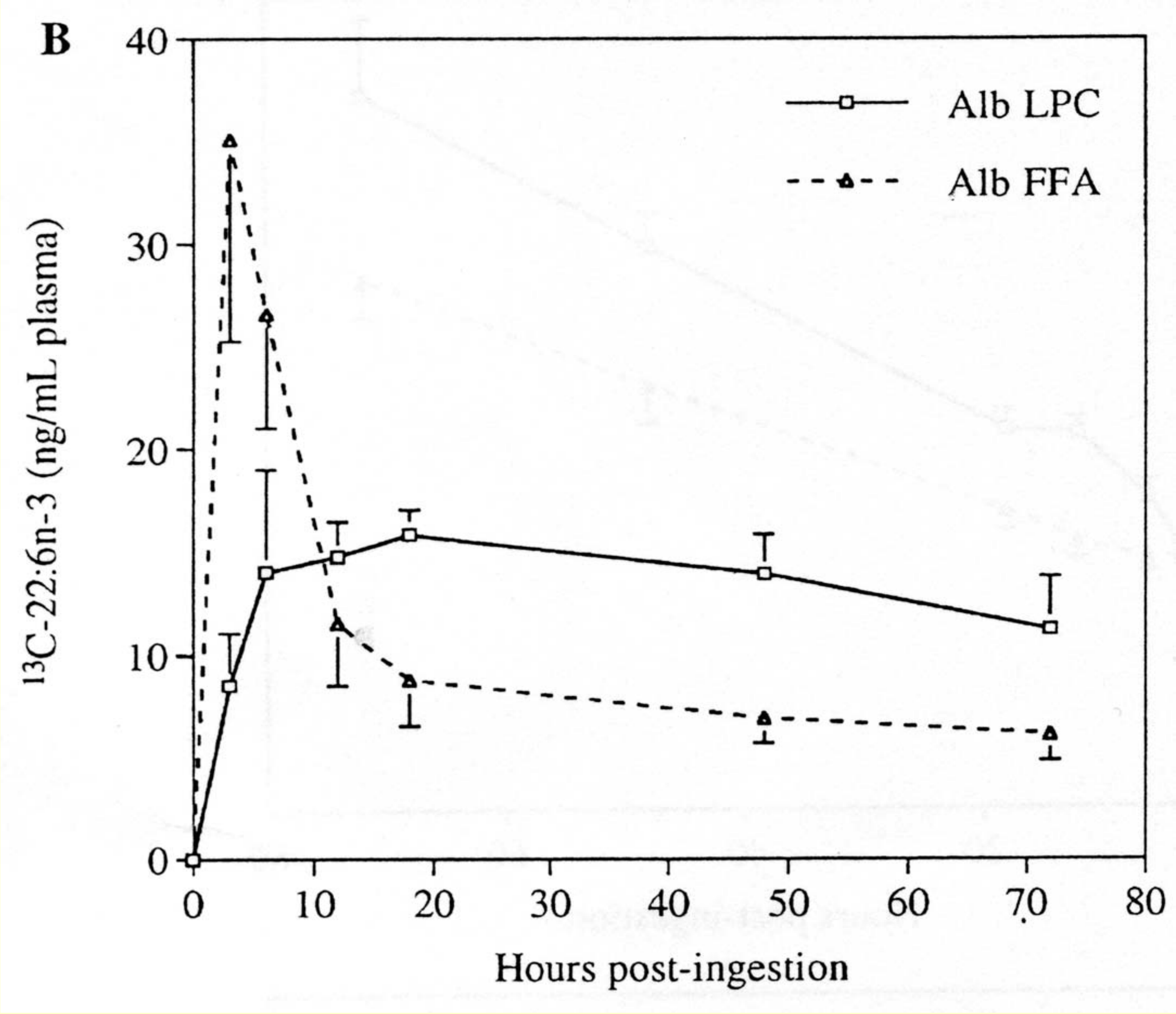
Thiès et al Am. J. Physiol. 1994

Conclusion (1)

The uptake of DHA by the brain, like other unsaturated fatty acids, was more efficient when esterified in LysoPC (1-lyso,2-DHA-GPC) compared to unesterified DHA.

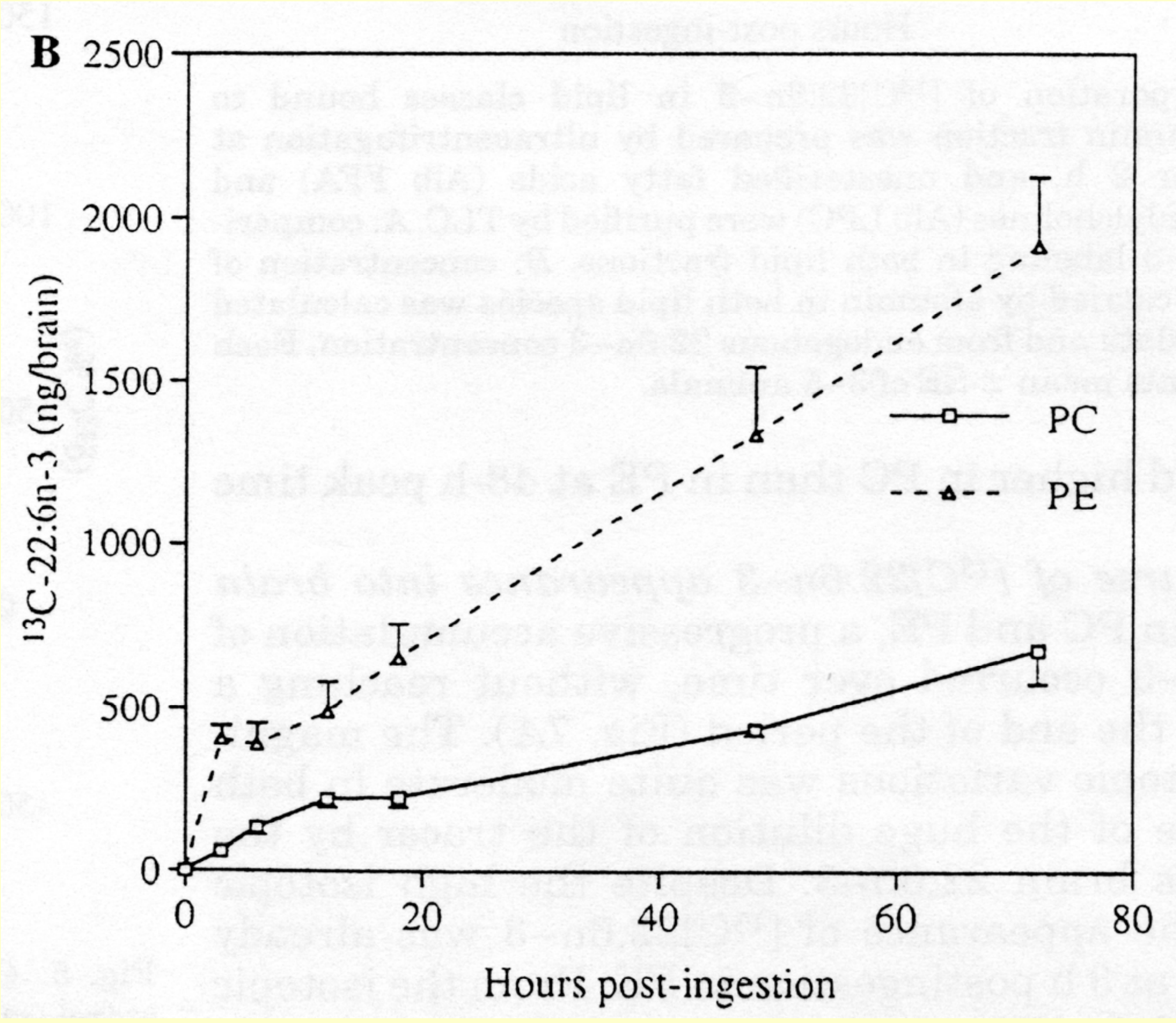
This preferential uptake was not valid with some other organs such as the heart and liver, with even a preference for unesterified DHA.

TG-DHA intake in the rat



Brossard et al. Am. J. Physiol. 1996

Brain accretion following **TG-DHA** intake



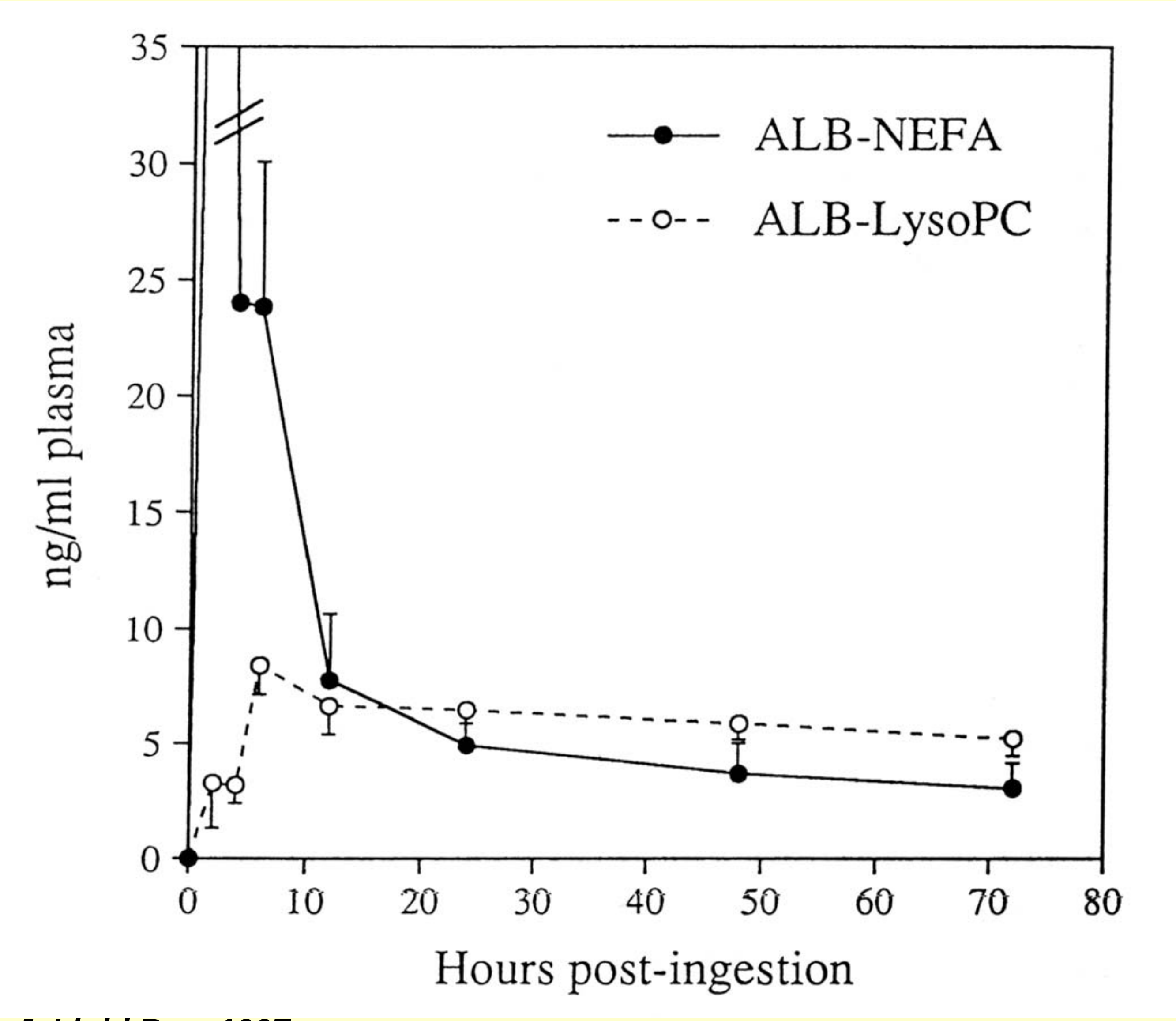
Brossard et al. Am. J. Physiol. 1996

Conclusion (2)

Intake of DHA (given in a triglyceride to the rat) allowed DHA to circulate under 2 forms bound to albumin, non-esterified DHA (peaking at 3 hours post-intake) and LysoPC-DHA (plateauing from 6 hours with a gradual decrease from 18 hours post-intake).

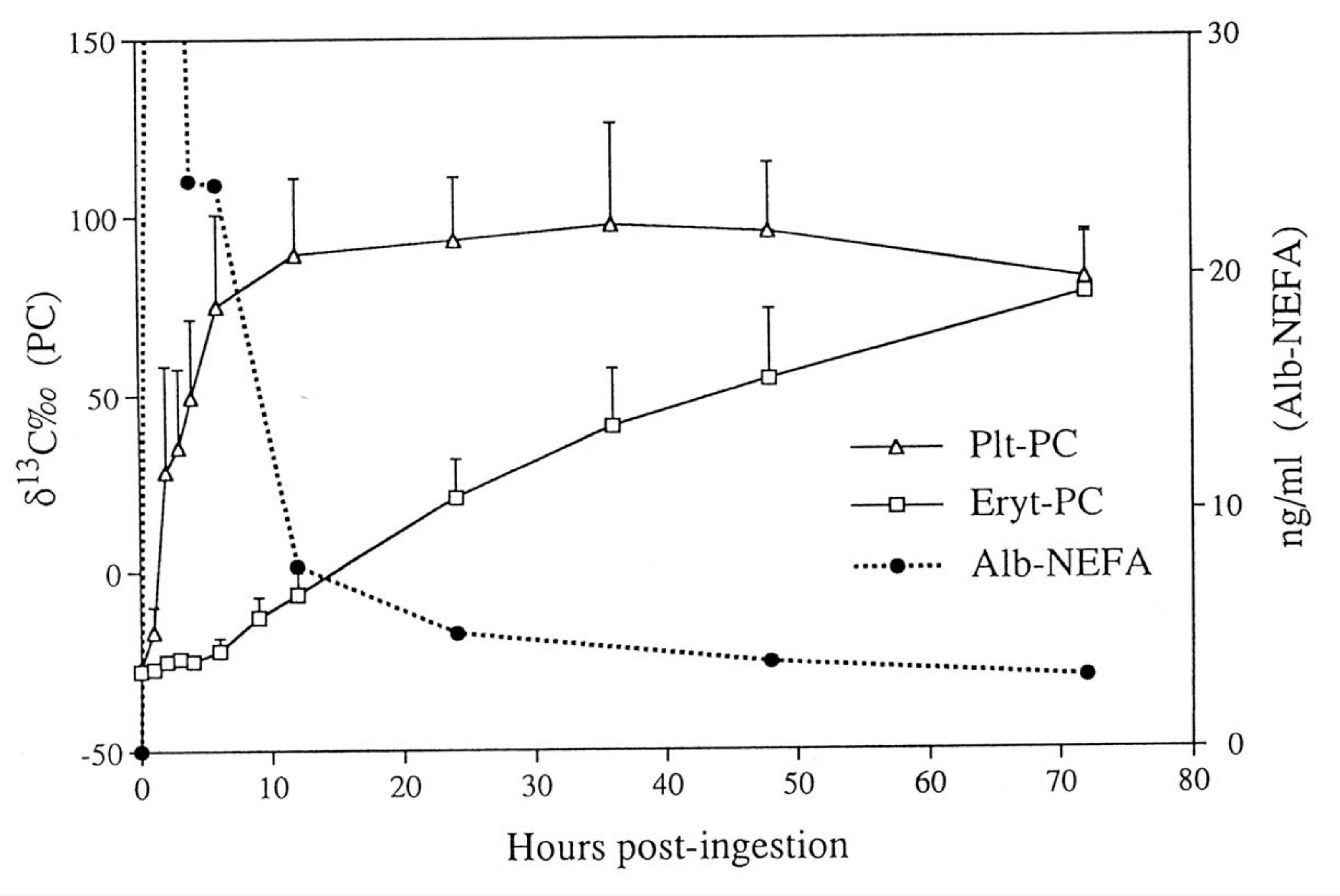
Incorporation of DHA into brain phospholipids gradually increased till 72h post-intake, which fits with LysoPC-DHA being a more efficient vehicle than non-esterified DHA.

TG-DHA intake in humans



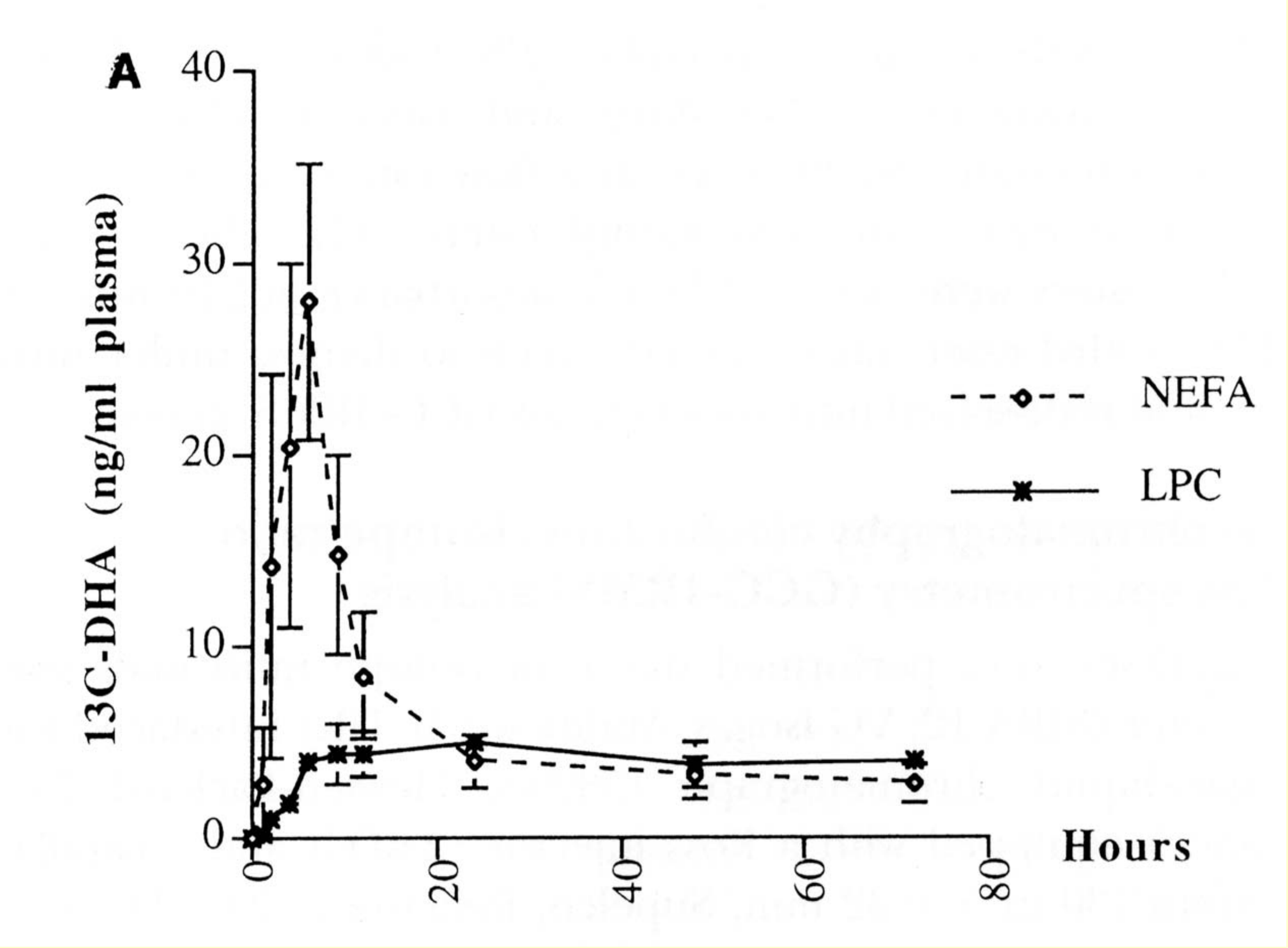
Brossard et al. J. Lipid Res. 1997

Blood distribution of DHA following TG-DHA intake



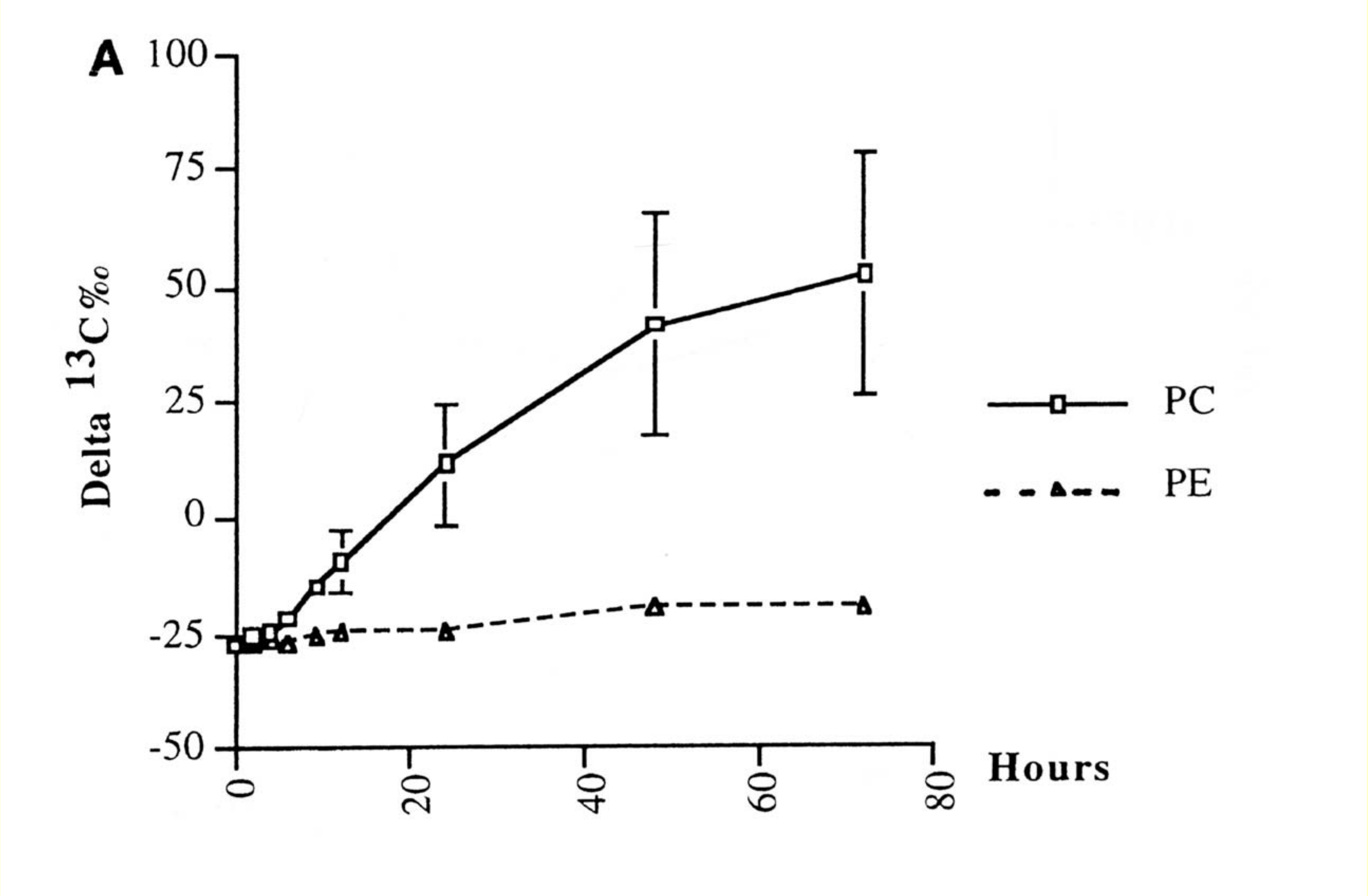
Brossard et al. J. Lipid Res. 1997

Blood distribution of DHA following PC-DHA intake



Lemaitre-Delaunay et al J. Lipid Res. 1999

DHA incorporation into erythrocyte PL following PC-DHA intake



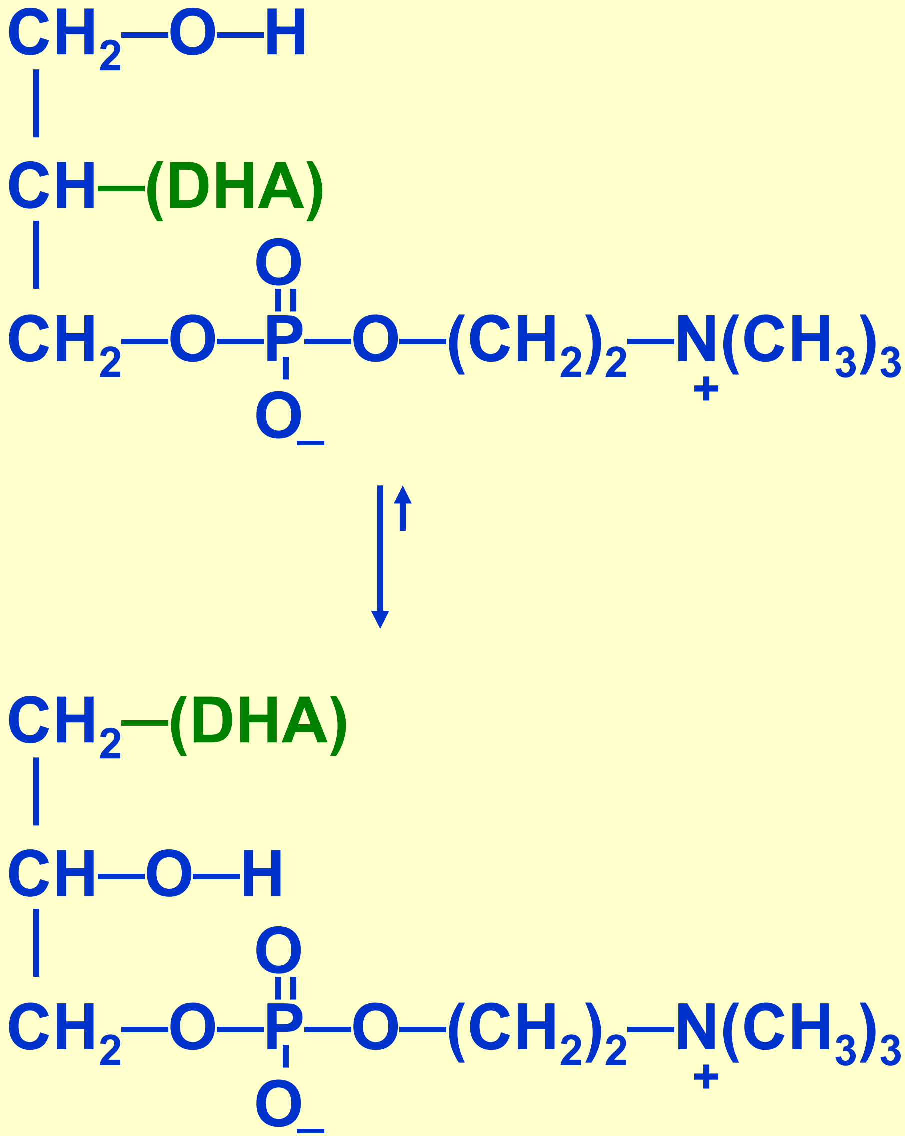
Lemaitre-Delaunay et al J. Lipid Res. 1999

Conclusion (3)

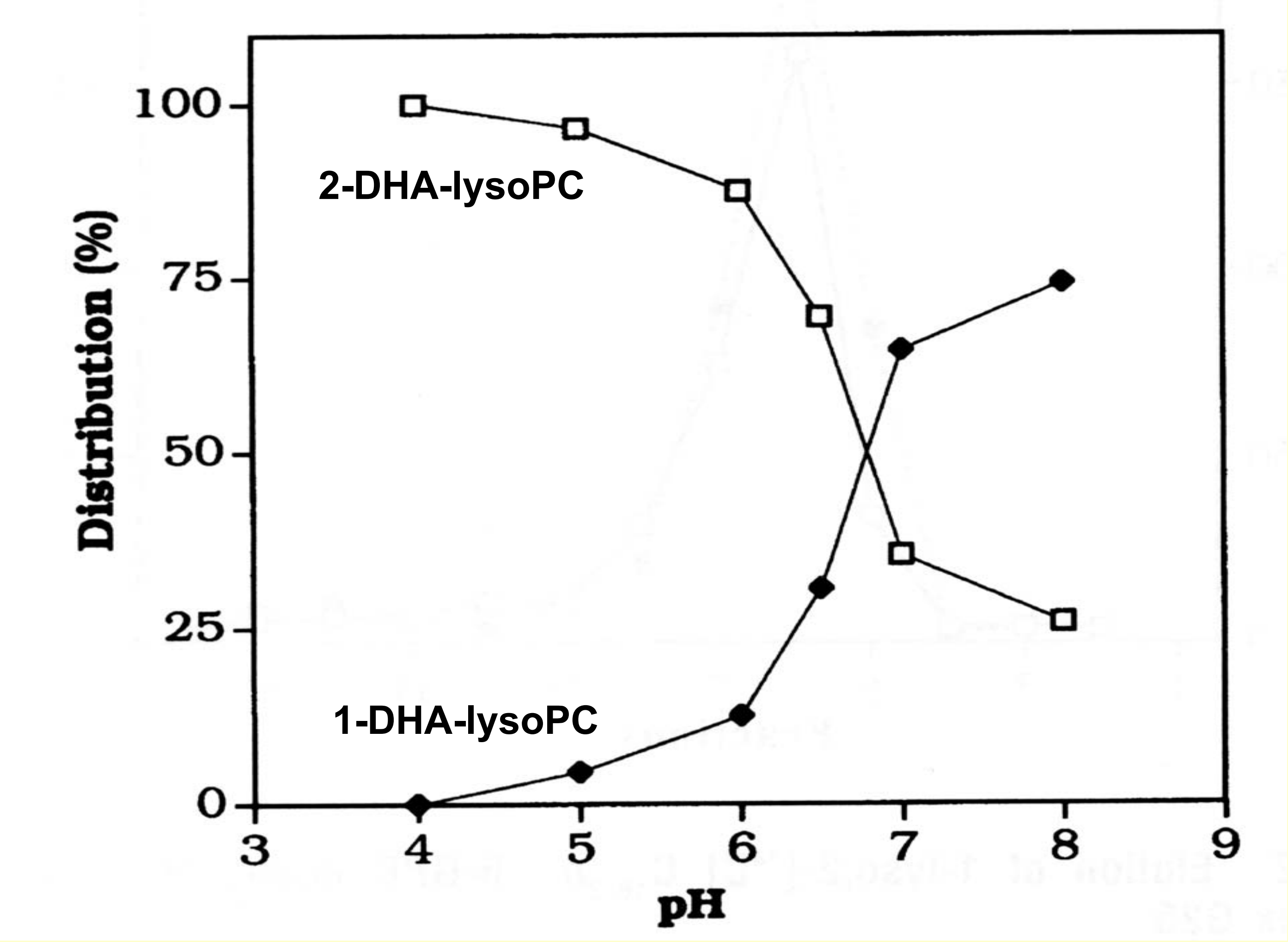
In humans, intake of TG-DHA led to similar pattern as in rats for DHA and LysoPC-DHA bound to albumin.

DHA incorporation in red blood cells (as an index of brain accretion) constantly raised in PC after a lag phase of around 6 hours, again fitting with LysoPC-DHA as the main source of DHA.

The intake of PC-DHA in place of TG-DHA led to similar patterns except for a delayed peak of non-esterified DHA in plasma.


CH2—O—H
CH—(DHA)
CH2—O—P—O—(CH2)2—N(CH3)3
CH2—(DHA)
CH—O—H
CH2—O—P—O—(CH2)2—N(CH3)3

Conversion of 2-DHA-lysoPC into 1-DHA-lysoPC within 20 min.



Croset et al. Biochem. J. 2000

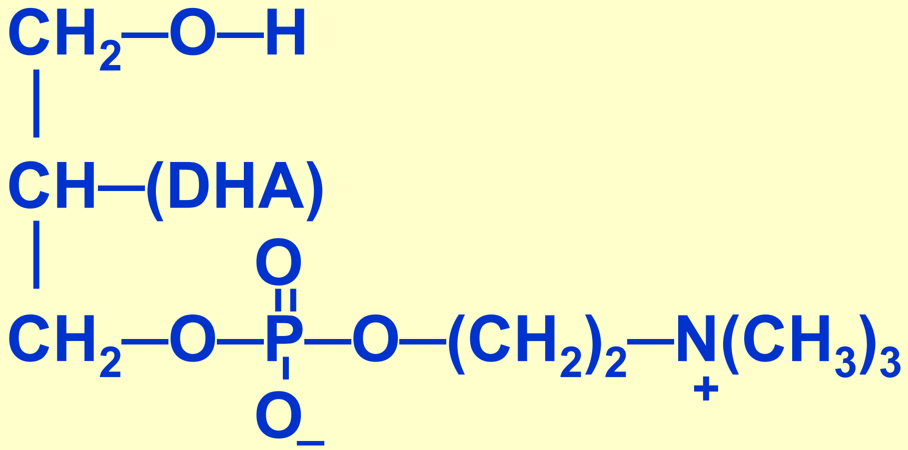
	Proportion (%)	
Species	1-Lyso,2-acyl-GPC	1-Acyl,2-lyso-GPC
Rat	55 ± 13	45 ± 12
Human	41 ± 12	56 ± 11

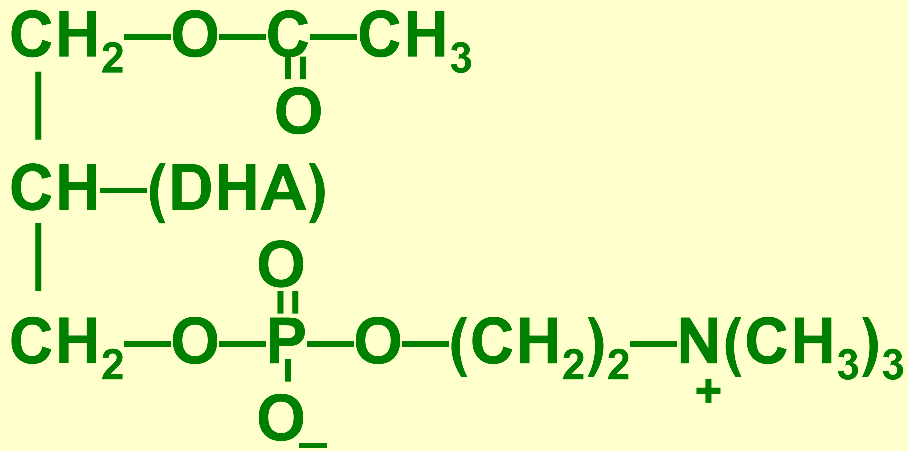
Croset et al. Biochem. J. 2000

Conclusion (4)

Polyunsaturated LysoPC, including LysoPC-DHA, circulates bound to albumin.

Although 1-lyso,2-DHA-GPC rapidly isomerizes into 1-DHA,2-lyso-GPC, around 50% of each form were measured, which means that the main produced form of LysoPC is the former (1-lyso,2-DHA-GPC).





Acetyl,Docosahexaenoyl-GPC (AceDoPC)

Patent N° 92/14078.

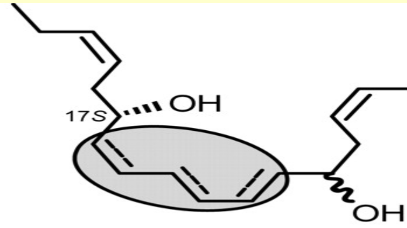
Patent N° 06/09929.

Neuroprotectin D1 (NPD1)

Neuroprotectin D1, also called protectin D1, is a dihydroxy-docosatriene (docosanoid) issued from DHA, namely 10,17*S*-diOH-4*Z*,7*Z*,11*E*,13*E*,15*Z*,19*Z*-22:6.

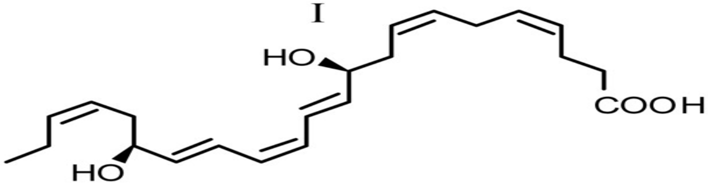
It could derive from the oxygenation of DHA by 15-lipoxygenase, and act as a potent anti-inflammatory and neuroprotective agent.

Mukherjee et al PNAS 2004 ; Lukiw et al JCI 2005 ; Bazan TN 2006 ; Levy et al JI 2007



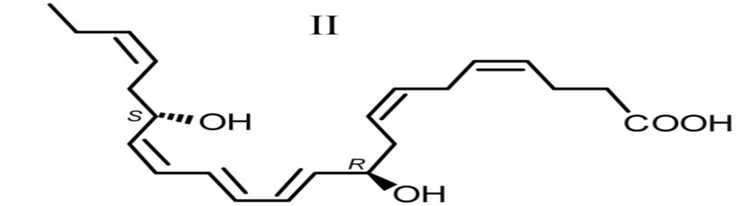
PD1

I



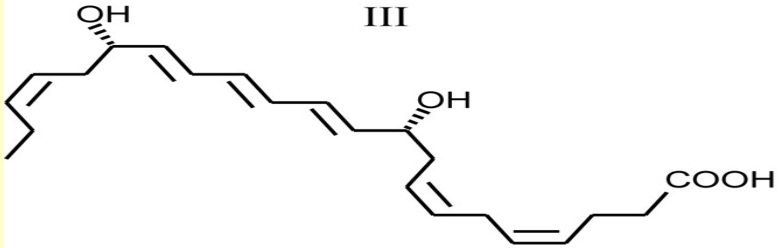
10*S*,17*S*,-dihydroxy-docosa-4*Z*,7*Z*,11*E*,
13*Z*,15*E*,19*Z* hexaenoic acid

II



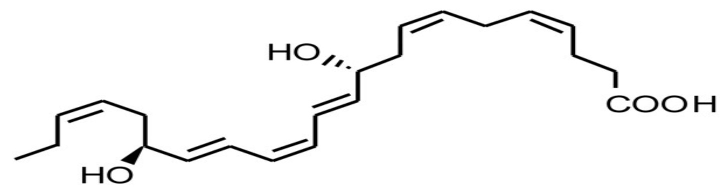
10*R*,17*S*,-dihydroxy-docosa-4*Z*,7*Z*,11*E*,
13*E*,15*Z*,19*Z*-hexaenoic acid

III



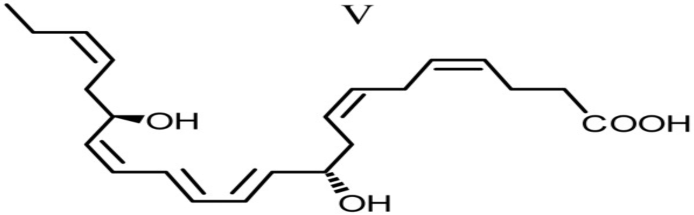
10*R*,17*S*,-dihydroxy-docosa-4*Z*,7*Z*,11*E*,
13*E*,15*E*,19*Z* hexaenoic acid

IV



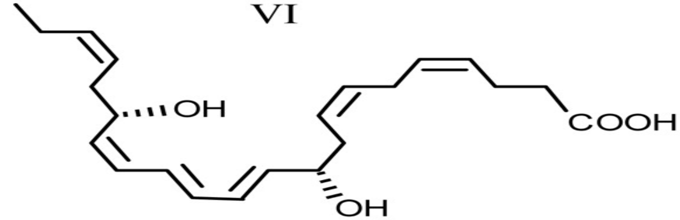
10*R*,17*S*,-dihydroxy-docosa-4*Z*,7*Z*,11*E*,
13*Z*,15*E*,19*Z*-hexaenoic acid

V



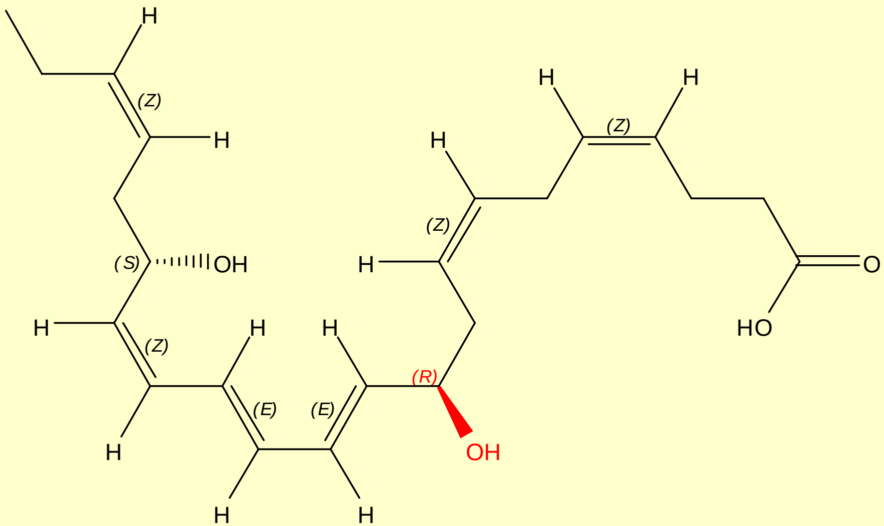
10*S*,17*R*,-dihydroxy-docosa-4*Z*,7*Z*,11*E*,
13*E*,15*Z*,19*Z*-hexaenoic acid

VI

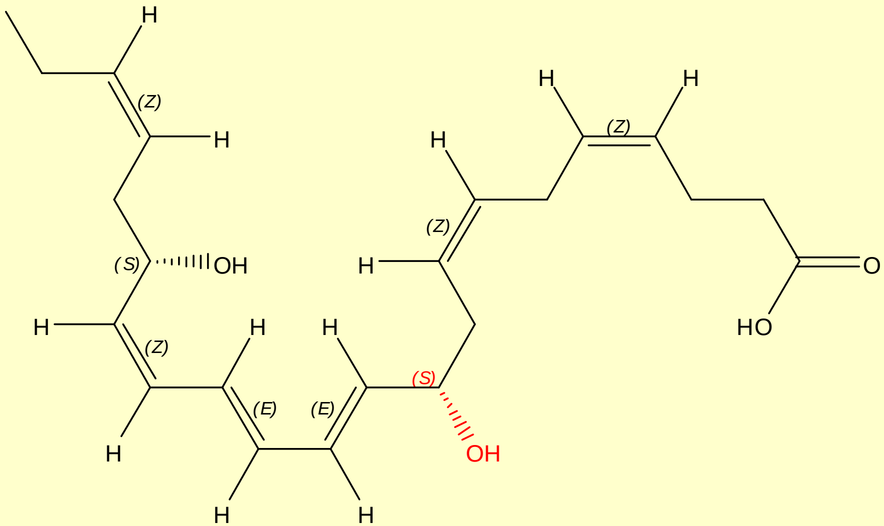


10*S*,17*S*,-dihydroxy-docosa-4*Z*,7*Z*,11*E*,
13*E*,15*Z*,19*Z*-hexaenoic acid

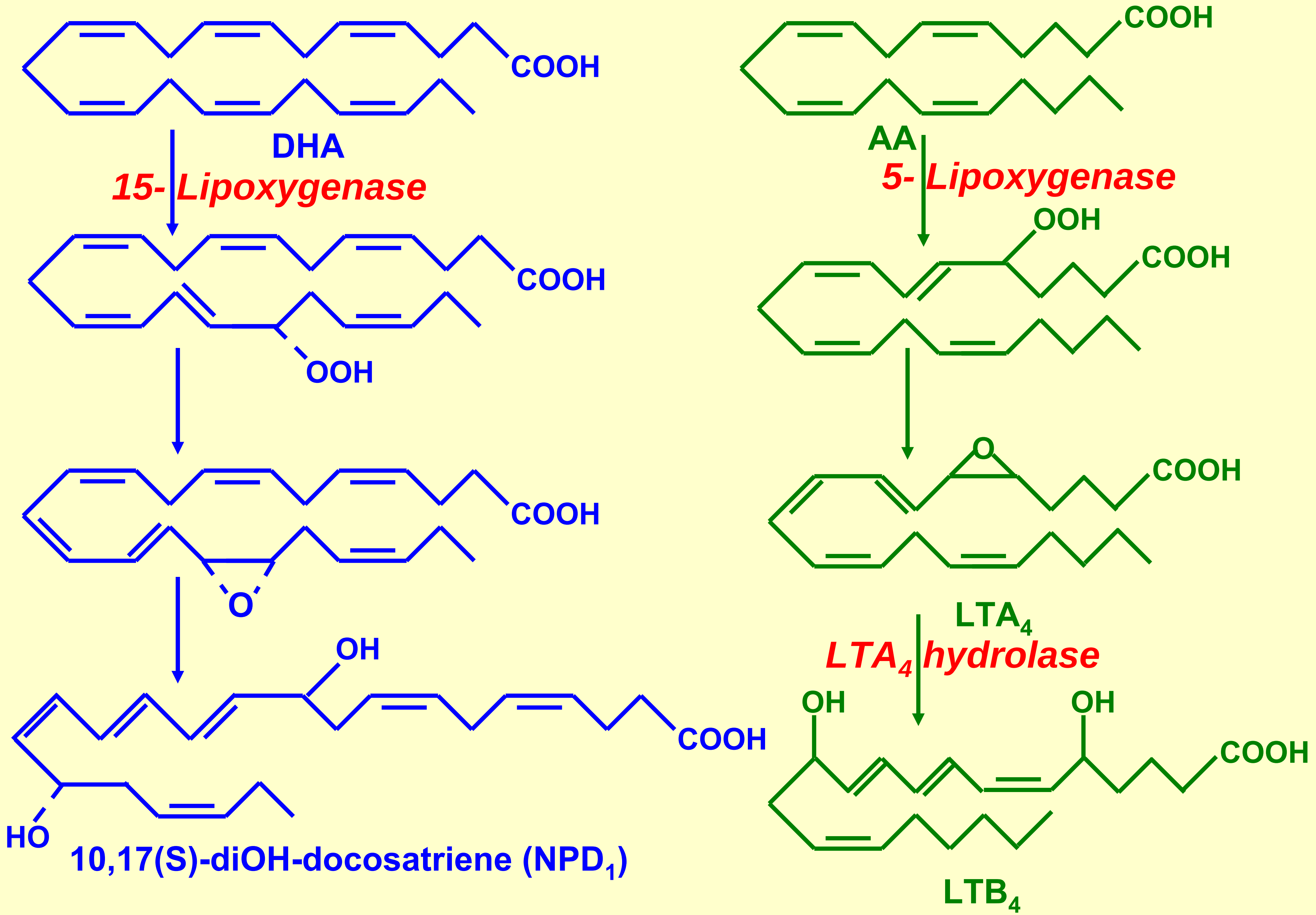
Serhan et al. JI 2006



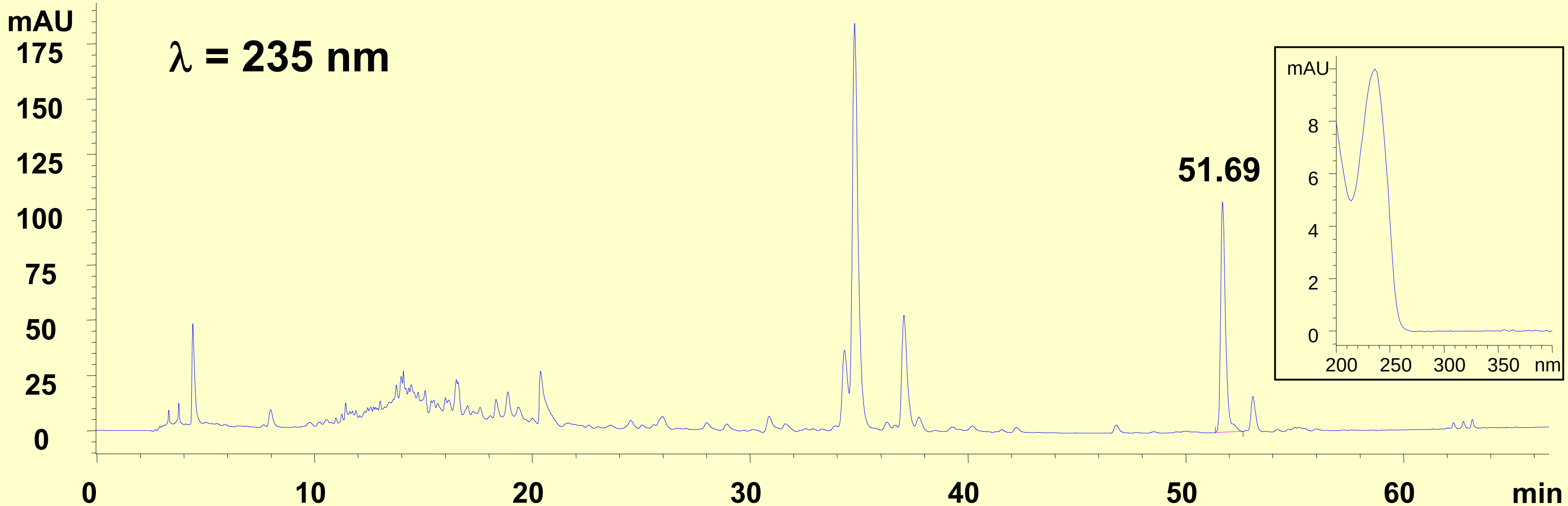
10R,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid



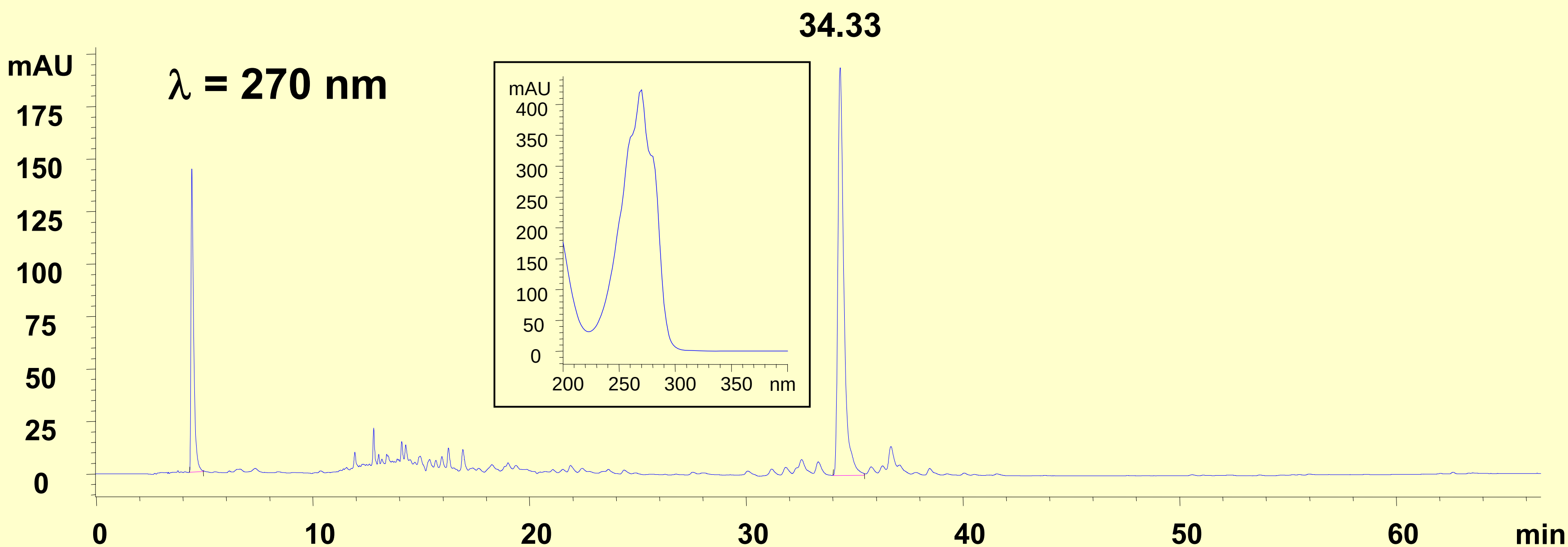
10S,17S-dihydroxy-docosa-4Z,7Z,11E,13E,15Z,19Z-hexaenoic acid



COOH
DHA
15- Lipoxygenase
COOH
OOH
COOH
O
OH
COOH
HO
10,17(S)-diOH-docosatriene (NPD1)
COOH
AA
5- Lipoxygenase
OOH
COOH
O
COOH
LTA4
LTA4 hydrolase
OH
OH
COOH
LTB4



λ = 235 nm
mAU
175
150
125
100
75
50
25
0
51.69
0
10
20
30
40
50
60
min
mAU
8
6
4
2
0
200
250
300
350
nm



λ = 270 nm
34.33
mAU
175
150
125
100
75
50
25
0
0
10
20
30
40
50
60
min
mAU
400
350
300
250
200
150
100
50
0
200
250
300
350
nm

SUMMARY

LysoPC-DHA might be an important vehicle of DHA to the brain.

The form which is assumed to be esterified in the brain, 1-lyso,2-DHA-GPC, represents around 50% of the two circulating forms, although the most stable one is its isomer 1-DHA,2-lyso-GPC.

We have prepared 1-acetyl,2-DHA-GPC (AceDoPC), to stabilize DHA at the sn-2 position, with AceDoPC closer to LysoPC-DHA than to DHA-containing PC.

Neuroprotectin D1 can be obtained by treatment of DHA with 15-lipoxygenase, which can be extended to AceDoPC as a substrate.

Brossard Nicole
Croset Martine
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Thiès Frank

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Guichardant Michel
Michaud Sabine
Picq Madeleine

Doutheau Alain