Conclusions

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First of all, I would like to emphasize the quality and the richness of all the presentations. We had the chance at this joint DGF/AFECG meeting, to have experts from different and complementary domains & labs.
I'm not at all a brain specialist or a physiologist, nor am I a nutritionist. My job is to select good sources of fats & oils and to find technical & chemical parameters for their uses in Danone Biscuits & Dairy Products. So I learnt a lot during these 2 days! I will try to sum up the main issues; please forgive me in advance if I missed some points.

PUFA metabolism

We directly entered the key role of PUFA with Pr Crawford who highlighted the unique importance of DHA in the evolution of species, and in the evolution of brain. In his view, it seems that *Nature* has selected DHA instead of DPA because of one extra double bond, which allows the molecule to better interact with proteins in cell membranes. DHA provides brain cells with a unique fluidity. So what could seem a detail conditions the structure and the activity of our brain.
We can draw a link with Pr Cunnane's book, *Survival of the Fattest* in which he proposed that seafood DHA boosted the brain power of early humans, so the fattest could became the fittest. The production of DHA in our body appears limited, even if we have in our diet a sufficient amount of precursors like ALA. So, the knowledge of the various metabolism stages of PUFA in the nervous cells is essential.
Drs Guesnet and Alessandri presented data on cultured cells; it seems that there is no limit for DHA incorporation, but limits for producing DHA from ALA, EPA or DPA are probably due to the peroxisomal desaturation step.

PUFA for brain development in early life

In the presentations from Drs Demmelmair and Pawlosky, we saw the importance of Omega 3 and Omega 6 intake during pregnancy and post-natal period, with impact on short term & long term brain development; even if the newborn has the capacity to synthesize DHA from ALA, and ARA from LA.
DHA & ARA are both crucial for the optimal development of the brain and the eyes.
Dr Demmelmair showed data suggesting a preferential transfer of DHA from blood to placenta, with the help of Fatty Acid Transer Protein 4. In the placenta DHA is present mainly in the form of phospholipids.
Dr Pawlosky proposed an interesting compartimental model for Omega 6 pathways in newborns, showing turnover, intake and synthesis.
At the cellular level, Dr Vancassel and Dr Benjamin Buaud, reported animal studies with diet modifications (deficient or not in ALA). Dr Vancassel explained that a DHA deficit in neuronal membranes has an impact on neurotransmission. B. Buaud showed us that modifications in nuclear receptor expression due to Omega 3 deficiency, would lead to modifications of synaptic plasticity. In fine, this could induce some behaviour modifications.

PUFA and aging disorders

Alzheimer's disease has been studied for over one hundred years but its prevalence continues to increase like our lifespan in industrialized countries. Once again, DHA plays a specific and key role in the appearance and evolution of the disease.
Pr Cunnane referred to the recent work of Pr Guesnet on DHA in brain glucose transport, and highlighted the fact that the brain has a specific metabolism, particularly for ketone use when glucose availability is low. Brain DHA level seems to be an important regulator of brain glucose uptake, particularly for the elderly. It's also of importance to understand the role of insulin in brain glucose metabolism.
Pr Hartmann reviewed the complicated regulation between gamma secretase/Amyloid Precursor Protein/Amyloid beta, and the link with lipid homeostasis. It is noteworthy that Amyloid β is involved in sterol and sphingolipid metabolism. This could lead to new approaches for the prevention and treatment of Alzheimer Disease ('AD). A high level of DHA in the diet reduces the formation of amyloid plaques.
In the same direction, Thierry Pillot reported the neuroprotective effect of DHA enrichment and fish consumption in Alzheimer Disease development. Dr Bryhn presented the results of the first intervention study showing evidence for the positive effect of supplementation with concentrated fish oil rich in DHA on the reduction of memory decline at early stages of AD.
Dr Heurtaux focused on alphalinolenic acid (ALA) impact highlighting the molecular mechanism of neuronal protection induced by ALA via the activation of a specific potassium channel, the 2 pore domain channel TREK1. In an animal model, ALA activated TREK1, and reduced induced ischemia & epilepsy. It can also play a cerebral preconditioning role.
Finally, yesterday Dr Acar discussed the impact and mechanisms of omega 3 in the retina which contains the highest concentration on this fatty acid. The eye reflects the importance of getting the right kind of fat and DHA with positive impact on retinal diseases.

PUFA role in behaviour troubles and related pathologies

We began with Dr Barberger-Gateau's presentation on epidemiological data, which suggested a combined protective effect of long chain Omega 3 and anti-oxidants against cognitive decline & dementia.
She reported also a significant protective effect from the consumption of oil rich in omega 3 (rapeseed and nuts) and a deleterious effect caused by an excess of Omega 6. This was a good link between yesterday's presentations on AD, and the following topics on pathologies.
Dr Astrog reviewed the data available regarding the link between Omega 3 intake or status and mood disorders like depression. It seems that a moderate supplementation with EPA combined with an anti depressor treatment is more effective than a DHA supplementation.
With Dr Vamecq, we had a cellular level view of the impact of a ketogenic diet (used for epilep-

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tic patients) on astrocyte/neuron interactions. It emphasizes again the specific metabolism in the brain, especially under unusual feeding conditions.

Dr Pages' presentation on Omega 3 from rapeseed oil showed the results of an animal study with magnesium deficient mice (epilepsy model), revealing that a chronic diet rich in ALA has a protective effect on neuronal disorders such as epilepsy. As already mentioned, interactions between fatty acids and proteins are key in the understanding of brain health and disease. Pr Spener shared a review on current knowledge on fatty acids binding proteins (FABPs) in the brain. The possible use of these molecules as diagnostic markers was highlighted. FABPs allow DHA to move into the cell. Without this help, DHA will stay in the membrane.

Then we were pleased to listen to the Medaille Chevreul lecture by Dr Stanley Rapoport, who showed how DHA is provided to our brain, with the help of the liver, even when dietary conditions are difficult (omega3 deficient diet: no intake of ALA). The brain is an organ totally dependent on DHA, as it does not possess desaturases. We also saw amazing images of human brain obtained by positron emission tomography showing AA & DHA consumption.

Perspectives

The bioavability of LCPUFA present in our diet will determine their level in our brain. Pr Parmentier insisted on the interest of having PUFA in phospholipids form, especially in sn2 position. Then he presented an original patented ingredient extracted from salmon brain, the *Phospho-Lipo-Proteic-Complex*. So we can claim "directly from salmon brain to the human brain"...

As we all require DHA in our diet, and as the world population is still growing, we can wonder whether the marine sources of DHA would be sufficient to meet human needs. In his talk, Dr Abadi highlighted the possibility for PUFA production by transgenic plants.

Pr Lagarde re-emphasized the role of phospholipids and of DHA as the precursor of neuroprotectin D1, which has potent anti-inflammatory and cell-protecting properties.

Conclusion

One could have called this congress "Omega 3 & brain", or even "DHA & brain" because evidence relates this fatty acid to our individual development and that of our species. PUFA are key for the construction of the cerebral structures during pregnancy and for their maintenance as we age. We now have more than hope for the prevention and treatment of Alzheimer disease, through the understanding of the molecular & cellular basis of the disease, and the role of PUFA.

During these 2 days, we shifted several times from human to animal and cellular levels. PUFA and especially DHA are key for membrane fluidity, and for exchanges between the cell and its environment. Consequently they are key in exchanges between human beings. Because DHA is difficult to synthesize in our body, even with good precursor quantity & quality, our brain has set up strategies of economy and recovery of DHA.

But we should not forget the complementary roles of other PUFA, and the importance of the ratio between Omega 3 and Omega 6. We also saw the importance of protein in PUFA metabolism.

Our diet affects the chemistry of our brain, and could influence our mood and behaviour. Something as simple as eating fish several times a week, and using rapeseed or flaxseed oils, could help our brain functions and our social life. The bio availability of PUFA is also of interest.

Thanks again for your participation, and I hope that we all get "fat enough" to survive! Take care of your DHA!