Omega 3 Fish Oil with Purified Eicosapentanenoic Acid Also Stimulates Cerebral Perfusion
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Abstract

Background: Omega-3 fish oil stimulates cerebral perfusion by a prostaglandin-independant mechanism as shown by animal studies. We reported at the International Conference on Alzheimer's Disease in Madrid, Spain, 2006 that acid ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) or Lovaza, stimulated cerebral perfusion. Owing to possibly more favorable effects of purified EPA (Vascepa) on serum lipids, not only decreasing serum triglycerides but also increasing serum high-density lipoprotein and decreasing low density lipoprotein (LDL) vs. Lovaza which increases LDL, it is likely that Vascepa will be used increasingly.

Methods: Brain SPECT used 70 MBq Tc-99m-HMPAO and a Siemens ECAM with an ultra-high resolution (5.9 mm) collimator for basal and 8 grams oral EPA-stimulated images obtained after 45 minutes. To verify the cortical metabolic index (CMI) from SPECT, a Siemens ECAT Exact 47 with 5 mm resolution and 20 MBq F-18 fludeoxyglucose (FDG). We verified a cerebral flow reserve index (FRi), the difference of a cortical perfusion index (CPI) and CMI, as a measure of cerebral perfusion in humans by comparing multiple known perfusion stimulants, including 0.8 mg sublingual nitroglycerin, 500 mg IV acetazolamide, 50 grams oral coconut oil and 10 grams oral Lovaza, all of which produce FRi (10+-2)% in near normal subjects.

Results: A 57 year-old diabetic woman with minor memory complaints had CMI 59.0% by SPECT and FRi (8.4+-2.1)% when imaged fasting and normoglycemic. The regionally differential stimulant effects of purified EPA were shown in a 69 year-old traumatic brain-injured (TBI) man with mild cognitive impairment, whose CMI was (65.2+-2.2)% by FDG PET and (70.7+-3.5)% by SPECT. His post EPA FRi of -(6.8+-2.7)% correlated with decreased bilateral parieto-occipital and bilateral mesial temporal perfusion tracer deficits which is not unusual in TBI patients and similar to metabolic deficits in Alzheimer's disease. Similar results were obtained with 10 grams oral Lovaza after 3 hours or 50 grams oral coconut oil after 60 to 90 minutes.

Conclusion: Purified EPA omega 3 fish oil has favorable effects on serum lipids and also remarkable effects on cerebral perfusion with potential for significance in both diagnosis and therapeutics of cognitive impairment.
Fig. A: Cortical Metabolic and Perfusion Index Method.

Axial SPECT or PET slices acquired after tracer injection in a quiet, dark room, are parallel to the brain long axis from occipital to prefrontal. For the Cortical Metabolic index (CMi), one or more axial slices are centered one third of the way from the top of the brain, just superior to the roof of normal-sized lateral ventricles. The PET image protocol used a 5 min transmission scan and a 15 min emission scan with acquisitions beginning no sooner that 30 min after tracer injection. Activity display is a Sokoloff color scale, with white for peak brain, black for zero and spectral colors for intermediate activities. Isocontour enclosed areas contain activity > specified percentages of peak activity. In an axial slice, a 6% isocontour represents total brain activity comparable to that seen with attenuation corrected PET and a 60% isocontour represents cortical activity, the ratio of these two 60% isocontour activity/6% isocontour activity = CMi representing the fraction of total activity due to cortical activity.

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Fig. 1: Basal (bottom of each of three paired rows of images) and nitroglycerin stimulated (top of each of three paired rows of images) brain SPECT for a 29 year-old insulin resistant man with cognitive dysfunction, including learning disabilities and minor memory complaints, who also suffers from chronic migraine headaches and experienced multiple episodes of head trauma kick boxing from age 19 to 23 years.

Note absence of cerebral flow reserve, FRi - 0.2% with nearly equal CMi 66.9% and CPi 66.7% similar to 181 insulin resistant patients age 52.7+-15.0 years with primarily memory complaints, who had average FRi - (0.057+-7.60)% and 293 patients with history of traumatic brain injury, age 52.0+-14.2 years with average FRi (0.01+-7.66)%. 
2. Fig. 2: Follow-up brain SPECT of the now 33.6 year-old man from Figure 1 with migraine headaches and difficulty concentrating using 8 grams of Vascepa (EPA) as the perfusion stimulant which increased FRi to 6.21% with CMi 62.99% and CPi 69.20%.

This patient had remarkable improvement in concentration and resolution of headaches, noted by himself as well as his family and co-workers, when treated twice daily with a supplement containing approximately 3 grams EPA and 8 grams medium chain triglycerides from coconut oil.
Fig. 3: Saggital SPECT views reveal cerebellar, cortical and basal ganglia stimulation in a 72 year old woman with multiple stroke and dementia risk factors including: age > 70 years, hyperlipidemia, hyperglycemia due to uncontrolled type 2 diabetes mellitus (HbA1c 12.2%), stage 3 chronic kidney disease (estimated GFR 36 ml/min/1.73 meter sq), primary hypothyroidism with high TSH 9.61 (normal 0.45 to 4.5 mIU/ml) and associated hypothalamic pituitary axis abnormality (low growth hormone suggested by borderline low IGF-1 of 42 ng/ml with normal 36-166 ng/ml).

The cerebral flow reserve index, FRi was 17.0% after 8 grams oral EPA, greater than the 95% confidence limits FRi of (5.80-15.18)% in 41 near-normal patients age 51.3±14.1 years who received usual cerebral perfusion stimulants such as 0.8 mg nitroglycerin sublingual or 500 mg acetazolamide IV.
Fig. 4: Effect of 8 g EPA stimulant in a 40 year-old woman with memory loss, mild hypothyroidism and high-titer antithyroid peroxidase antibodies. Patient has CMI 59.5% and CPI 52.77% with an FRi of -6.73% vs. values (5.80-15.18)% in 41 near normal patients. Decreased FRi occurs in multiple conditions including: cerebrovascular, renal or pituitary disease, hypertension, neurotoxin exposure, diabetes mellitus, insulin resistance (IR), traumatic brain injury (TBI) or autoimmune cerebritis, in this case, likely due to thyroid-associated autoimmune cerebritis.
Fig. 5: Regionally differential stimulant effects of purified EPA were shown in a 69 year-old traumatic brain-injured (TBI) man with mild cognitive impairment, whose CMi was (65.2+/-2.2)% by FDG PET (a representative axial view shown on the left below) and 57.79% by SPECT using Tc-99m-HMPAO (with a basal image shown below a perfusion stimulated image below on the right). The SPECT normalization used a comparison of average white matter activity and peak brain activity, the ratio of (peak brain)/(average white matter) being 2.506 in this patient and similarly 2.522 ± 0.189 in 11 near normal patients. His post EPA FRi of -11.2% correlated with bilaterally decreased parieto-occipital (particularly on the left) and bilateral mesial temporal perfusion tracer deficits which are not unusual in TBI patients and similar to metabolic deficits in Alzheimer's disease. Negative FRi, reflecting more prominent deficits with perfusion stimulation, is typical to TBI patients who have pituitary disease and in fact this patient had hypogonadotrophic hypogonadism, the most common pituitary deficit post TBI in our experience which now includes over 300 patients with persistent symptoms averaging at least two years, approximately 40% of whom have hypothalamic-pituitary abnormalities.
**Summary**

Dementia is a clinical syndrome whose etiology is multifactorial. Multiple interrelated dementia risk factors coexist but may not have equal or simply additive pathophysiologic effects nor equal influence on quantitative biomarkers of dementia. Among the dementia risk factors, including cerebrovascular disease, hypertension, diabetic or nondiabetic insulin resistance (which tend to coexist with obesity), and even traumatic brain injury and neurotoxic metal exposure, there is a common denominator of cerebral hypoperfusion. Brain SPECT, particularly using protocols that compare basal metabolism and stimulated perfusion, is well suited to detect cerebral hypoperfusion while brain PET with FDG glucose provides an excellent measure of basal cerebral metabolism. We focused not only on absolute measures but also the cerebral flow reserve (FRi), defined as the difference of Cortical Perfusion and Metabolic indices (CPi minus CMi). Renal dysfunction is of increasing interest as a dementia risk factor, particularly in light of its well recognized pathophysiologic interactions with hypertension, insulin resistance, and metal toxicity and our results are corrected for effects of renal dysfunction which are parabolic, normal renal function correlating with maximal, normal FRi and FRi decreasing with either renal hyperfiltration or renal insufficiency.

Although treatment results remain preliminary, agents that relieve cerebral hypoperfusion have positive effects. These include antihypertensives, vasodilators such as nitrates and cilostazol (recently recognized as effective stroke prevention in diabetics), coconut oil and medium chain triglycerides from coconut oil, as well as omega-3 unsaturated marine oil either purified EPA or mixtures of primarily EPA and DHA. Moreover, in both diabetics and nondiabetics, agents with positive modulation of glucose metabolism and possibly other neuroendocrine effects on body weight, including incretins, also have both acute and chronic effects on regional and global cerebral perfusion.