

# **DEPRESSION AND SCHIZOPHRENIA: ESSENTIAL FATTY ACIDS AND OTHER ESSENTIAL NUTRIENTS**

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# FISH, SEAFOOD AND DEPRESSION

- **Studies from the US National Institutes of Health show that in countries where fish and seafood consumption are high, the prevalence of depression is low**
  - **major depression**
  - **bipolar depression**
  - **post-partum depression**
- **In the US and Finland individuals who eat fish and seafood are at much less risk of depression and suicide than people who rarely or never eat fish and seafood**

# WHAT IS SPECIAL ABOUT SEAFOOD?

- **Contains an excellent balanced quantity of almost all essential nutrients, especially selenium**
- **The major dietary source of long chain omega-3 essential fatty acids (EFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)**
- **Omega-3 fatty acids make up about 8% of the brain by weight**

# ARE OMEGA-3 EFA LEVELS ABNORMAL IN DEPRESSION?

## Direct Evidence

- In blood samples from North America, Europe, Australia and Japan, depressed individuals have lower amounts of DHA, and especially low amounts of EPA, as compared to normal individuals

## Indirect Evidence

- Low levels of EPA lead to an increased risk of thrombosis and cardiac rhythm abnormalities
- Depressed patients have abnormal cardiac rhythm, hyperactive platelets and a greatly increased risk of heart disease and diabetes

# WHICH OMEGA-3 IS MORE IMPORTANT IN DEPRESSION?

- The brain has much more DHA than EPA but EPA is much more important in responses to nerve stimulation: DHA may be more important for structure and EPA for function
- EPA is more abnormal than DHA in blood samples from depressed patients
- In a randomised, controlled trial at the University of Sheffield, DHA was slightly worse than placebo whereas EPA was much better
- In a study at Baylor University, DHA was again slightly worse than placebo
- EPA is the most important fatty acid in depression

# **TWO RANDOMISED CONTROLLED TRIALS OF PURE ETHYL-EPA (LAX-101) IN TREATMENT-UNRESPONSIVE DEPRESSION**

- **Both studies used ultra-pure ethyl-EPA since the purer the compound the more effective it seems to be**
- **Nemets et al in Israel compared placebo with 2g/d in patients who had initially responded to standard drugs but who had then relapsed**
- **Peet and Horrobin investigated 70 patients who had failed to respond to standard drugs in a study which compared placebo with 1g/d, 2g/d or 4g/d ethyl-EPA: best dose was the lowest at 1g/d**

**NEMETS STUDY IN ISRAEL**  
**(now published in the March 1<sup>st</sup>, 2002 issue of the**  
**American Journal of Psychiatry)**

	<u>PLACEBO</u>	<u>ETHYL-EPA</u>
Baseline Hamilton Depression Score	22.3	24.0
Change over 4 weeks	-2.3	-11.6
Patients improving by FDA criteria	1/10	6/10
Statistical significance of difference	p<0.001	

**Patients have continued since on E-EPA and shown  
progressive further improvement**

# PEET AND HORROBIN STUDY IN THE UK

(now accepted and about to be published in Archives of General Psychiatry)

<u>Percentage of patients improving</u> <u>By FDA criteria after 12 weeks</u>			
	<u>Placebo</u>	<u>E-EPA</u>	<u>p</u>
Hamilton Scale (doctor)	25%	69%	0.001
MADRS Scale (doctor)	17%	62%	0.001
Beck Scale (patient)	25%	69%	0.003

Depression, anxiety, sleep, lassitude, libido and suicidality all improved

# HOMOCYSTEINE, DEPRESSION AND DEMENTIA

- Homocysteine is an oxidative by-product of methylation reactions
- Homocysteine levels are normally controlled by methylating it to methionine in a reaction dependent on folic acid and vitamin B<sub>12</sub>, or by converting it to cystathionine in a reaction dependent on vitamin B<sub>6</sub>
- Homocysteine levels are elevated in depression, schizophrenia, dementia, stroke and cardiovascular disease
- Folic acid, vitamin B<sub>12</sub> and pyridoxine are likely to be helpful in all these conditions

# DOES FOLIC ACID MAKE FLUOXETINE WORK BETTTER?

- 84 depressed women, all given fluoxetine (Prozac) and then randomised to receive 500 microg 1d folic acid or placebo

	<u>PLACEBO</u>	<u>FOLIC</u>
Patients improving by 50%	61%	94%
Patients completely recovered	47%	73%
Patients showing no response	17%	0%
Patients reporting side effects	30%	13%

# CONCLUSIONS: DEPRESSION

- In most pathologically depressed people, the major problem is nutrition
- Depression can usually be managed by
  - a high quality multnutrient supplement
  - extra folic acid, vitamin B<sub>12</sub> and pyridoxine
  - EPA at a dose of 500-1000mg, provided little or no DHA is present

# **SCHIZOPHRENIA AND TARDIVE DYSKINESIA: THE BIOCHEMICAL BASIS**

- **Much more complex than depression: at least three or four abnormal genes, and perhaps more, must be present simultaneously**
- **This must also mean that there are several different biochemical abnormalities, all of which must be present simultaneously**
- **There is now strong evidence for:**
  - **abnormal tryptophan pathway metabolism with an increased need for niacin**
  - **abnormal methylation reactions with elevated homocysteine and a toxic response to methionine**
  - **abnormal oxidation with defective glutathione metabolism and defective metabolism of catecholamines leading to adrenochrome**
  - **abnormal metabolism of arachidonic acid, an omega-6 essential fatty acid which makes up 6-7% of the brain by weight**

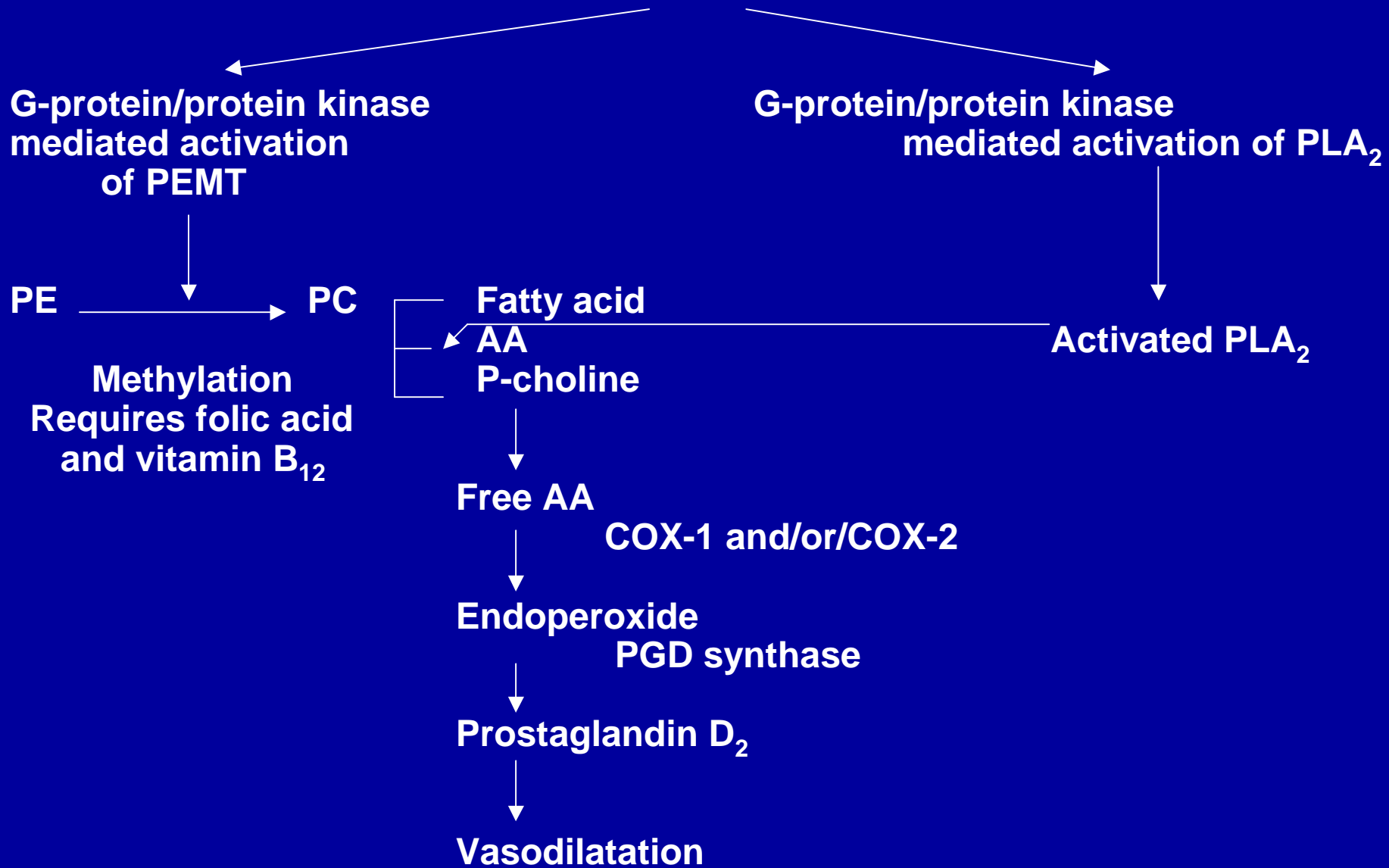
# **THE NIACIN SKIN TEST: OBJECTIVE EVIDENCE OF DEFECTIVE NIACIN RESPONSIVENESS AND ARACHIDONIC ACID METABOLISM**

- Normal people given more than about 200mg of niacin by mouth show dramatic flushing of the upper body
- Niacin does this by activating two reactions, phosphatidyl ethanolamine methylation and phospholipase A<sub>2</sub> activation
- Those mechanisms release arachidonic acid (AA) from membrane phospholipids
- AA is then converted to prostaglandin D<sub>2</sub> which produces skin flushing by dilating blood vessels
- About two thirds of people with schizophrenia – mainly those with “negative” symptoms – fail to flush normally on taking niacin

# THE TOPICAL NIACIN SKIN TEST

- The test can be made objective and consistent by applying different concentrations of niacin to the forearm skin
- There is concentration-related flushing which reaches a maximum level in 15-20 minutes
- In schizophrenia the flushing response is slow and the maximum effect is greatly reduced
- In other psychiatric disorders different results are obtained
  - in “positive” schizophrenia with no negative features the response is normal
  - in bipolar illness the response is normal or exaggerated
  - in major depression the early response is slow but the maximum effect is normal

# NIACIN RECEPTORS



# THE NIACIN TEST: SOME NEW FINDINGS

- Every investigator has found the test abnormal in a proportion of schizophrenic patients
- Similar findings have been noted in England, Scotland, Canada, the USA, Brazil, Australia, South Africa, India and Japan
- The abnormality is greatest at the time of first diagnosis when no drugs at all have been given: in Melbourne the test is being investigated as a technique of early diagnosis
- Medication, especially clozapine and EPA, may reduce the abnormality
- Patients and families like the test since it shows clearly that schizophrenia is a biochemical disorder

# THE EFA ABNORMALITIES IN SCHIZOPHRENIA

- **The main abnormality seems to be in arachidonic acid (AA) which is:**
  - **lost from nerve and other membranes more rapidly than normal**
  - **not incorporated back into membranes**
  - **oxidised abnormally easily**
- **All three abnormalities may be reduced by EPA**
- **However the best results will be obtained by a combination of**
  - **the Hoffer multinutrient regime, with particular emphasis on niacin, antioxidants and homocysteine lowerers**
  - **EPA**
  - **a very low dose of a standard antipsychotic**

# **EPA OR DHA AS ADD-ON TREATMENT IN SCHIZOPHRENIA (Peet et al, Schizophrenia Research 2001; 49:243-51)**

- **45 patients with chronic schizophrenia randomised to receive placebo; an EPA-rich oil (Kirunal); or a DHA-rich oil (Docanol): rated on the PANSS scale where new atypical neuroleptics produce an average improvement of 16%**

	<u><b>TOTAL PANSS</b></u>	<u><b>POSITIVE PANSS</b></u>
<b>Placebo improvement</b>	<b>10.7%</b>	<b>13.7%</b>
<b>Docanol improvement</b>	<b>9.5%</b>	<b>3.3%</b>
<b>Kirunal improvement</b>	<b>20.1%</b>	<b>23.8%</b>

# **EPA AS SOLE TREATMENT IN NEW EPISODE SCHIZOPHRENIA (Peet et al, Schizophrenia Research 2001; 49:243-251)**

- 26 patients with a new episode of schizophrenia randomised to receive Kirunal or placebo as sole treatment for 12 weeks: standard neuroleptics given as required

	<u>PLACEBO</u>	<u>KIRUNAL</u>
Percent reading standard neuroleptic	100%	57%
Percent managed on EPA alone	0%	43%
Average days on antipsychotic (max 84)	65	35
Percent improvement on total PANSS	28%	37%
Percent improvement on positive PANSS	28%	46%

# **EPA AS ADD-ON TREATMENT TO CLOZAPINE**

**(Peet and Horrobin, J. Psychiatric Research 2002; 36:7-18)**

- **16 patients with chronic schizophrenia who were treated with clozapine but were still ill were randomised to receive placebo or 2g/d ethyl-EPA (LAX- 101) for 12 weeks**

	<b>PLACEBO</b>	<b>E-EPA</b>
<b>Percent improvement in total PANSS</b>	<b>6%</b>	<b>26%</b>
<b>Percent improvement in positive PANSS</b>	<b>9%</b>	<b>26%</b>
<b>Percent improvement in negative PANSS</b>	<b>7%</b>	<b>24%</b>
<b>Percent improvement in general PANSS</b>	<b>3%</b>	<b>27%</b>
<b>Percent improvement in depression</b>	<b>11%</b>	<b>33%</b>

# **EPA AS TREATMENT FOR SCHIZOPHRENIA AND TARDIVE DYSKINESIA (Emsley et al, Schizophrenia Research 2002; 53:Suppl,1;9)**

- **40 patients with severe chronic schizophrenia and tardive dyskinesia were entered into a randomised, placebo-controlled trial of 3g/d ethyl- EPA (LAX-101)**

	<u><b>PLACEBO</b></u>	<u><b>E-EPA</b></u>	<u><b>p</b></u>
<b>Percent improvement in PANSS</b>	<b>3%</b>	<b>14%</b>	<b>0.03</b>
<b>Percent improvement in TD score</b>	<b>4%</b>	<b>69%</b>	<b>0.008</b>

# CONCLUSIONS: SCHIZOPHRENIA

- There are several biochemical abnormalities and so several corrective measures are required
- Some patients may be managed by nutrition alone using a regime which emphasises
  - broad spectrum nutritional correction
  - niacin
  - antioxidants
  - homocysteine-lowering agents
  - EPA
- In addition some patients may require an antipsychotic but usually at doses much lower than those normally prescribed