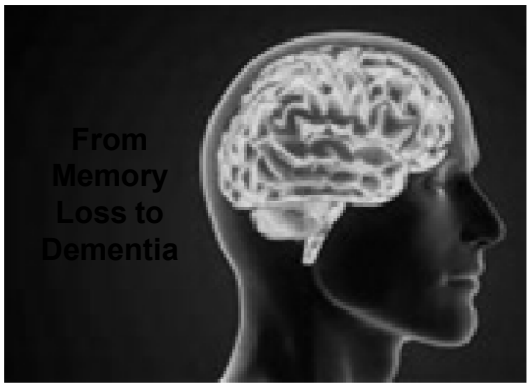

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PubMed now has 386,000 published articles on Epigenetics.

Epigenetics Ltd tel 01380 800105.

Topics to be discussed today.
What is memory – short and long term
Physiology of learning
Where is it stored
How neurotransmitters function at the synapse
Neurotransmitters involved with memory
ATP pumps to pump out Na and Ca
Importance of fatty acids in the neuronal cell wall
Trans neural degeneration – de-afferentation, infection, allergy, toxicity, deficiency
Energy production
ROS – oxidation of mitochondrial DNA
Mitochondrial DNA structure
APOE4
Methylation - Homocysteine
Hypoxia
GUT and Probiotics
How to examine a patient

Markers for examining people with Memory Loss
Amyloid beta protein fragment 1-42

ENERGY
Mg-ATP
DNA Polymerase
CoQ10 (Ubiquinone)
Complex III Cytochrome c reductase
Cytochrome C
Complex IV Cytochrome c oxidase
Cardiolipin
CO
CN
Malondialdehyde

HYPOXIA
O2
Hemoglobin
ALA
PBG
Uroporphyrin III
Coproporphyrin III
Protoporphyrin IX
Heme

Homocysteine
APOE4
Probiotics

What is Memory?

Memory is the process in which information is encoded, stored, and retrieved.

Encoding allows information from the outside world to reach the five senses in the forms of chemical and physical stimuli.

The loss of memory is described as forgetfulness or in serious cases, amnesia.

There are three main stages in the formation and retrieval of memory:

1. Encoding **or registration: receiving, processing and combining of received information**
2. Storage**: creation of a permanent record of the encoded information**
3. Retrieval**,** ***recall*** **or** ***recollection*****: calling back the stored information in response to some cue for use in a process or activity**

The Physiology of Learning

The Most Memorable Event in Living British History

The learning and remembering of such an event involved its
1. INTENSITY, FREQUENCY and DURATION

2. Coupled with the optimal synthesis of the appropriate neurotransmitter chemicals.

LEARNING

Can be divided into three phases

1. **Input**
2. **Storage**
3. **Output**

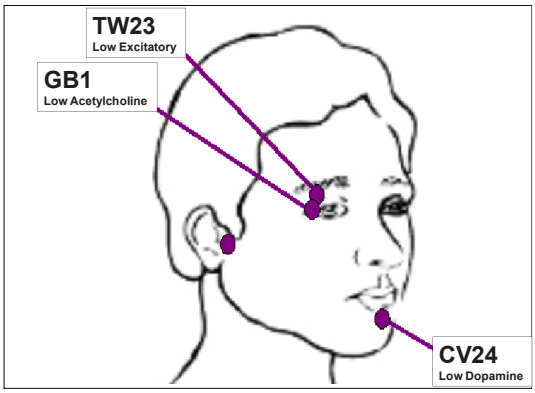
1. Input information is through our excitatory senses mediated by Glutamate.

2. We store our memories in the cortex and the hippocampus mediated by Dopamine.

3. Output is by recalling our memories via the hippocampus mediated by Acetylcholine.

Learning difficulties must therefore be due to either
1. Insufficient sensory stimulation or insufficient glutamate synthesis.
2. Insufficient dendritic connection or insufficient dopamine synthesis.
3. Insufficient cortical / hippocampal connections or insufficient acetylcholine synthesis.

1. **A deficiency in the excitatory neurotransmitter *glutamate* can be challenged for at TW23.**
2. **A deficiency of the neurotransmitter *dopamine* can be challenged for at CV24.**
3. **A deficiency of the neurotransmitter *acetylcholine* can be challenged for at GB1.**



Learning is a process that can be stopped, slowed or speeded up.

All that is necessary to speed up learning is stimulation to the 5 senses of vision, hearing, smell, taste and touch with increasing frequency, intensity and duration.

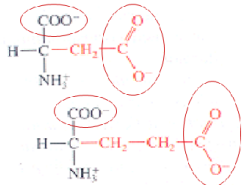
Glen Doman – Institutes of Human Potential

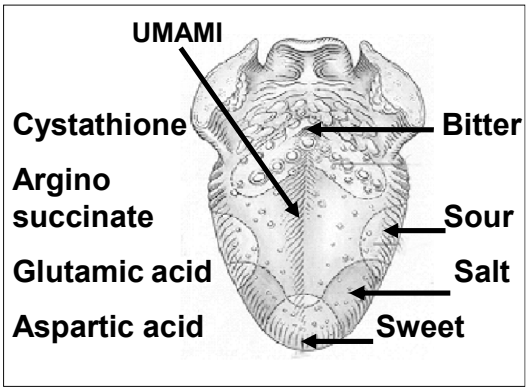
The sensory neurones of the 5 senses are all mediated by excitatory neurotransmitters. That is that they depolarise by permitting Ca++ ions to influx in addition to Na+.

Excitatory Neurotransmitters

Aspartic acid
(aspartate)

Glutamic acid
(glutamate)

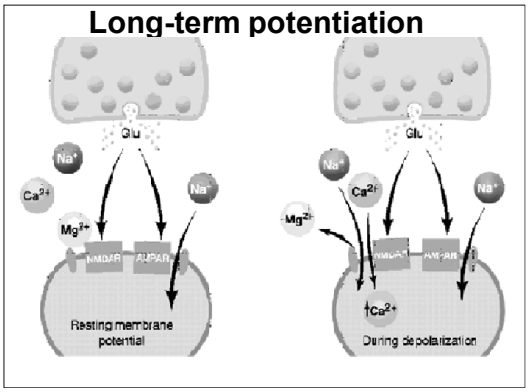


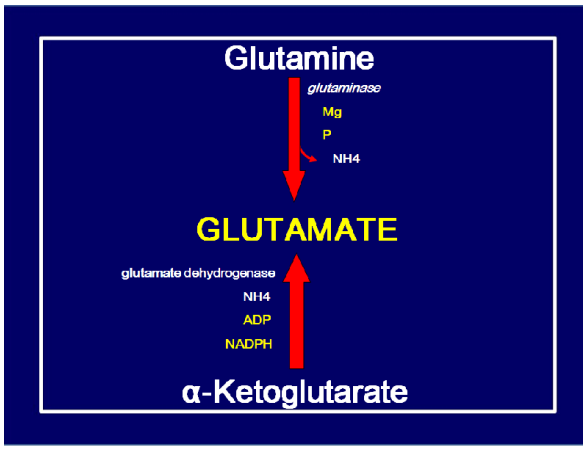


The NMDA glutamate sensitive receptor activation and the induction of long-term potentiation are thought to be necessary substrates for learning.

Glutamate receptors are also thought to play a critical role in the hippocampal long-term potentiation and the memory processes.

Long-term potentiation





Nutrients to consider for optimal GLUTAMATE synthesis

Glutamine
Mg++ and Phosphorus

NADPH (Vit B3)

Aspartic acid / Glycine / Mg++ (N.Methyl D. Aspartate 1000x times more active than glutamate)

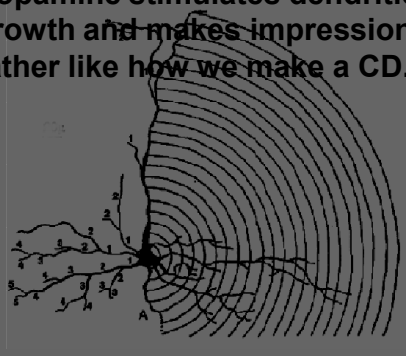
Challenge for 5 Senses Input

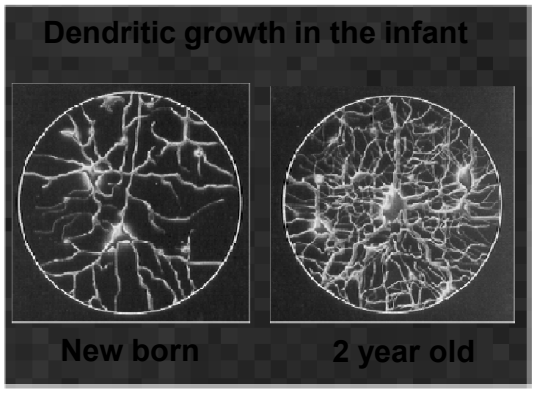
1. **Challenge each of the 5 senses right to left and then left to right.**
2. **Maintain positive TL and treat with Miron light in umbilicus for 1 minute.**
3. **Re-challenge remaining 4 senses etc.**

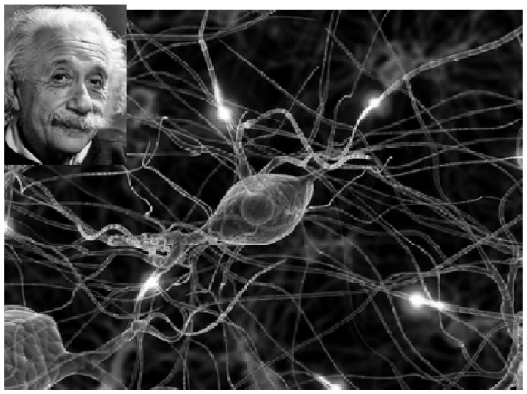
Challenging the 5 senses

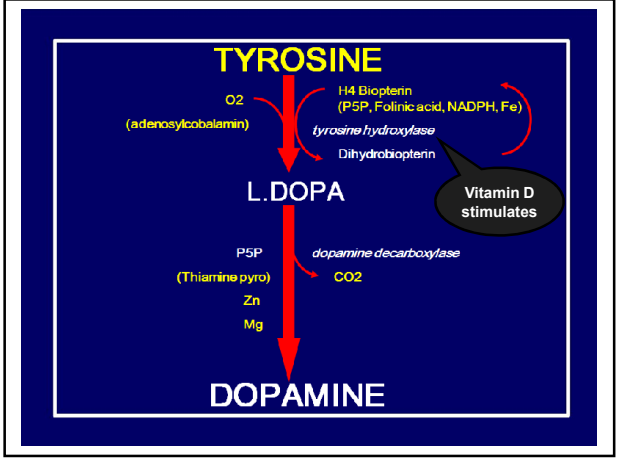
2. Memory is stored by dendritic connections modulated by dopamine

Dopamine stimulates dendritic growth and makes impressions rather like how we make a CD.




Dendritic growth in the infant
New born
2 year old



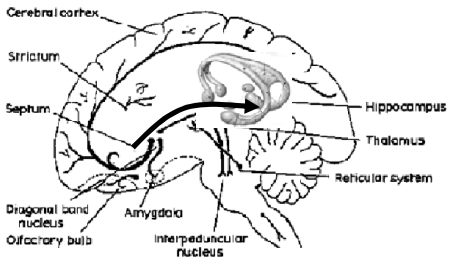

TYROSINE
O2
(adenosylcobalamin)
H4 Biopterin
(P5P, Folinic acid, NADPH, Fe)
tyrosine hydroxylase
Dihydrobiopterin
Vitamin D stimulates
L.DOPA
P5P
(Thiamine pyro)
Zn
Mg
dopamine decarboxylase
CO2
DOPAMINE

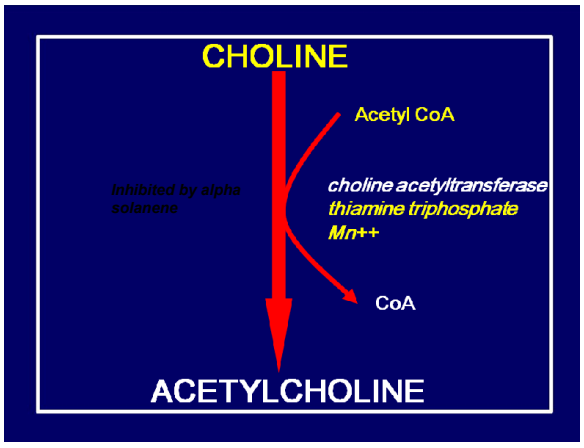
Nutrients to consider for optimal DOPAMINE synthesis

Tyrosine
O2, H4Biopterin (P5P, Folate, NADPH (Vit B3), Fe++), Vit D

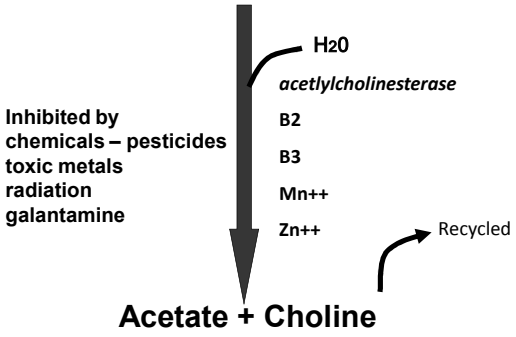
P5P (Vit B6) or Thiamine pyrophosphate (Vit B1), Mg++, Zn++

3. Memory recall involves adequate communication between the septum and the hippocampus

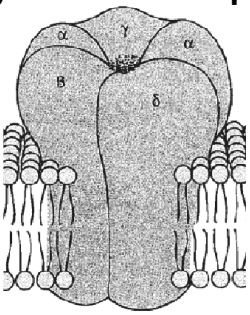




ACETYLCHOLINE

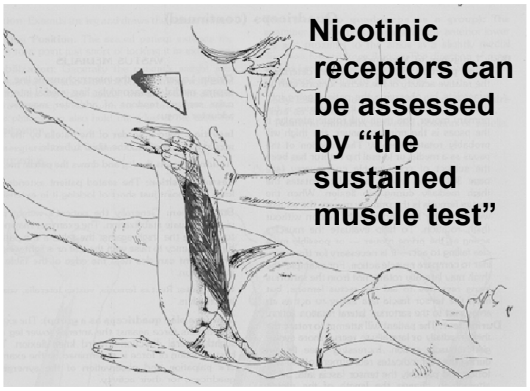


Acetylcholine Receptors



1. **Muscarine receptors occur in the parasympathetic nervous system**

2. **Nicotinic receptors occur at**
   i) CNS especially in the hippocampus.
   ii) The neuromuscular junctions



Nicotinic receptors can be assessed by “the sustained muscle test”

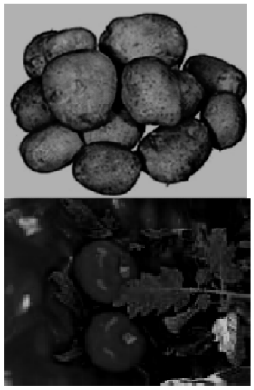
Natural sources of Acetylcholine

- Fennel
- Coriander
- Black pepper
- Hawthorn
- Fenugreek
- Cardamom
- Stinging nettle

Anticholinergics

Solanacea family

- Tomatoes
- Potato
- Bell peppers
- Aubergine
- Chili
- Tobacco



Nutrients to consider for optimal ACETYLCHOLINE synthesis

Choline
Acetyl CoA (Vit B5, Mg, Vit B6)
Thiamine triphosphate (Vit B1)
Mn++

No Potatoes, Tomatoes, Peppers, Aubergine, Chili

Non-threatening Learning / Remembering Challenges
Long term memory

Remember the first day at college.

Remember your 16th birthday.

Remember the first girl / boy you kissed.

What coloured eyes did he/she have

Short term memory

How many published articles on Epigenetics are currently on PubMed?

In which year was Epigenetics Ltd founded?

What is the telephone number of Epigenetics Ltd

Whilst maintaining the challenge if positive

1. **Cross therapy localise to TW23**
2. **Cross therapy localise to CV24**
3. **Cross therapy localise to GB1**

Challenge for negating nutrients.

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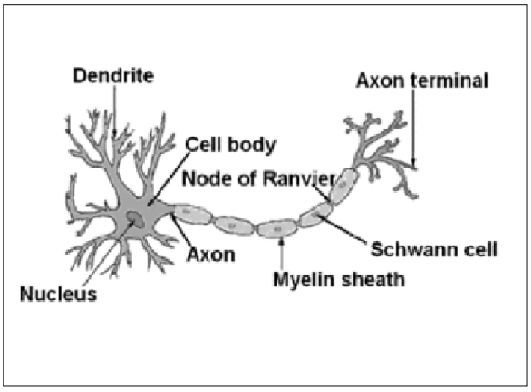
Dr. Williams, in collaboration with Dr. Warren H. Meck, associate professor in the Department of Experimental Psychology, opted to build an improved cholinergic system by adding choline to the diet when the cholinergic cells are being formed and making the synaptic connections in the brain.
Cholinergic cells are special because they need choline to make acetylcholine but cholinergic cells, like all cells, also require choline to maintain their cell membranes. "Thus, cholinergic cells doubly require choline," said Dr. Williams. So, Dr. Williams supplemented pregnant rats with choline in their drinking water.
This task taps into working and reference memories.
"Amazingly enough, the rats which had pre-natal or post-natal or both pre- and post-natal supplementation of choline made fewer mistakes on the first day of training and the choline animals continually perform better than control rats even as adults," said Dr. Williams. In fact, rats which had both pre- and post-natal supplementation of choline demonstrated the greatest amount of permanent improvement in their memory capacity and precision.
"Since those experiments were completed, the sensitive periods for choline administration have been determined to be prior to birth on days 12 to 17 in development and also days 15 and 30 after birth," said Dr. Williams.
The former period occurs when all the cholinergic neurons in the basal forebrain form. The latter period also seems to be highly significant because it is when these developing rats are being weaned and synaptic connections are being made in the hippocampus and cortex that are critical in visuospatial learning and memory.

In Human Terms
First 4 months of pregnancy
First 3 months of neonatal life

Prescribe 1500mg Choline bitartrate (delivering 600mg Choline)

Neurotransmitters



Neurotransmitters are chemicals made by neurons and used by them to transmit signals to the other neurons or non-neuronal cells

(e.g., skeletal muscle, myocardium, pineal glandular cells etc) that they innervate.

The neurotransmitters produce their effects by being released into synapses when their neuron of origin fires (i.e., becomes depolarized)

and then attaching to receptors in the membrane of the post-synaptic cells.

This causes changes in the fluxes of particular ions across that membrane, making cells more likely to become depolarized, if the neurotransmitter happens to be excitatory, or stimulatory or less likely if it is inhibitory.

Ten compounds -- belonging to three chemical families -- are generally believed to function as neurotransmitters somewhere in the central nervous system or periphery.

Excitatory	**Aspartic acid**
	Glutamic acid
Stimulatory	**Acetylcholine**
	Noradrenalin
	Dopamine
	Serotonin
	Histamine

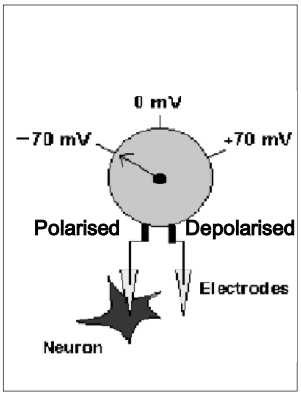
Inhibitory GABA, Glycine, Taurine

Glutamic acid and GABA are the most abundant neurotransmitters within the central nervous system, particularly in the cerebral cortex; glutamic acid tends to be excitatory and GABA inhibitory. Aspartic acid and glycine sub-serve these functions in the spinal cord.

Once released into the synapse, each neurotransmitter combines chemically with one or more highly specific receptors;

These are protein molecules which are imbedded in the post-synaptic membrane.

This interaction can affect the electrical properties of the post-synaptic cell, its chemical properties, or both.



When a Neuron is in its resting state, it sustains a voltage of about
- 70 mv
as the consequence of differences between the concentrations of certain ions at the internal and external sides of its bounding membrane.

Stimulatory neurotransmitters *(like Dopamine and Acetylcholine)* either open protein-lined channels in this membrane, allowing extracellular ions, like Sodium (Na+) to move into the cell, or close channels for potassium.

This raises the neuron's voltage towards zero, and makes it more likely that the cell will become depolarized. If the postsynaptic cell happens also to be a neuron (i.e., as opposed to a muscle cell), this depolarization will cause it to release its own neurotransmitter from its terminals.

The excitatory neurotransmitter glutamic acid, acting via its NMDA receptor, can also open channels for calcium ions (Ca++).

Excessive activation of these receptors in neurological diseases can cause toxic quantities of calcium to enter the cells, and kill them.

All Na+ and Ca++ has to be actively pumped out of the cell via the ATP pumps requiring energy.

Failure to do so leads to trans neural degeneration.

Trans neural degeneration may also be caused by

1. **De-afferentation**
2. **Infection**
3. **Allergy**
4. **Toxicity**
5. **Nutritional deficiency**

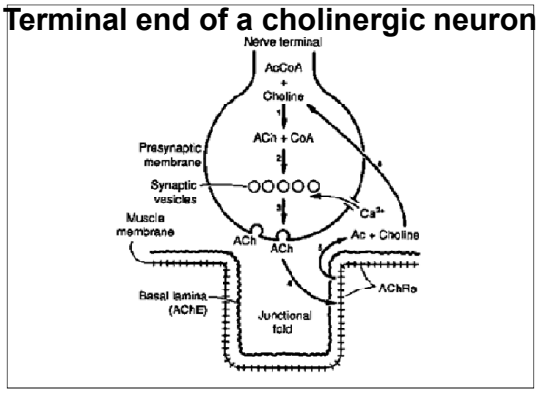
Once neurotransmitters have been secreted into synapses and have acted on their receptors, they are metabolised from the synapse either by enzymatic breakdown -- for example acetylcholine, which is converted to choline and acetate, neither of which has neurotransmitter activity.

For neurotransmitters like

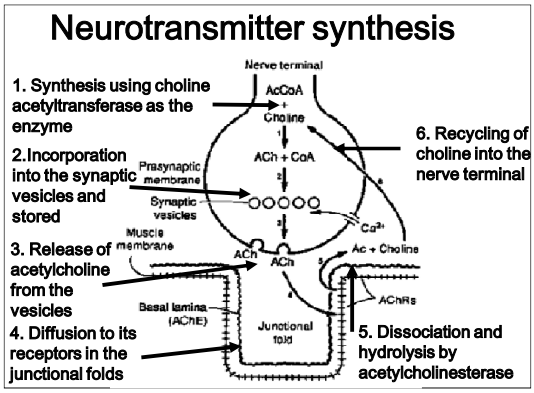
Dopamine
Serotonin
GABA

a physical process called reuptake takes place.

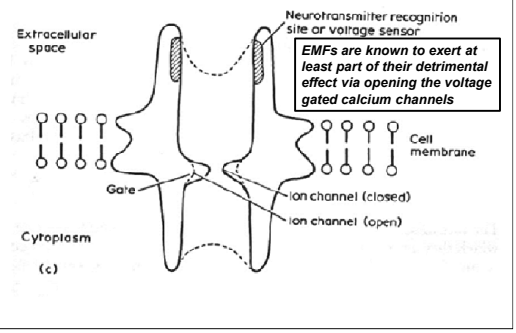
Terminal end of a cholinergic neuron



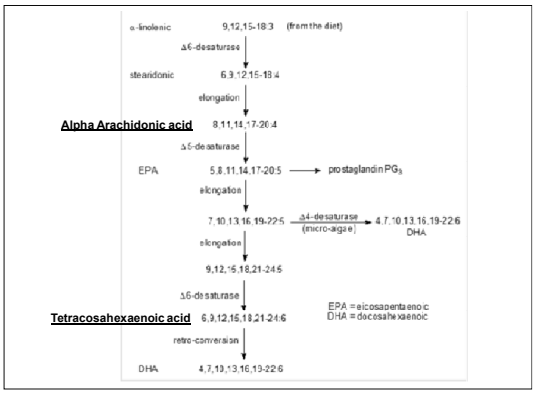
Neurotransmitter synthesis



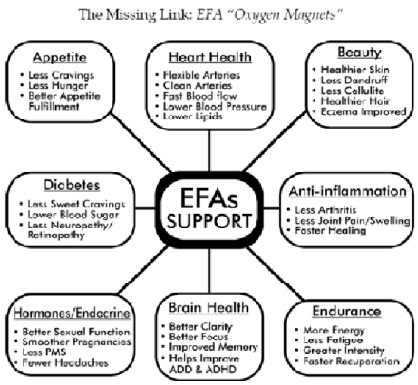
Receptors are like molecular ears



EMFs are known to exert at least part of their detrimental effect via opening the voltage gated calcium channels

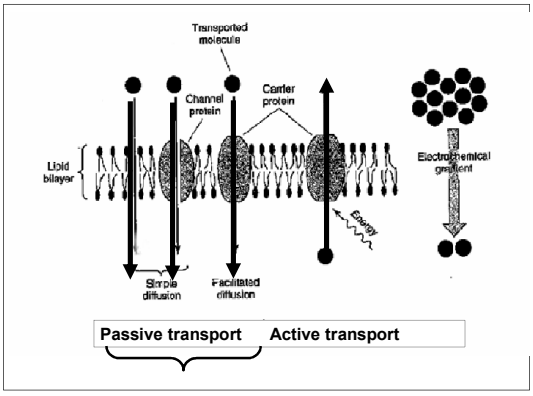


IMPORTANCE OF FATS FOR MEMORY AND DEMENTIA TREATMENT



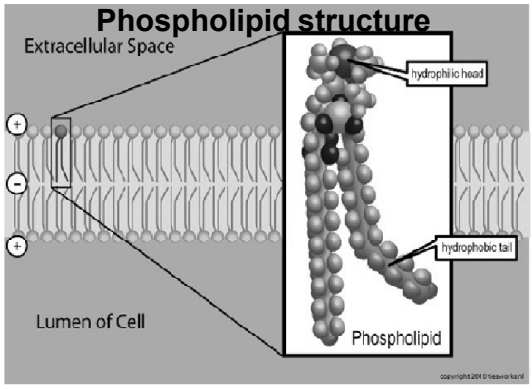
Cell Membrane

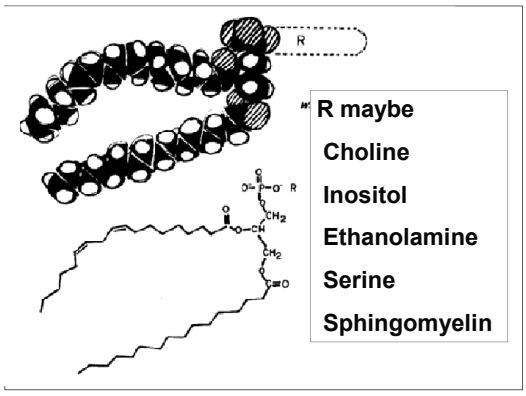
- **Transport of substances across the cell membrane**
- **Neurotransmitters – glutamate, dopamine, acetylcholine**
- **Sodium and calcium have to be pumped out of the cell**
- **Oxygen**
- **Require a flexible, permeable, fluid cell membrane**



Phospholipids

Phospholipid structure





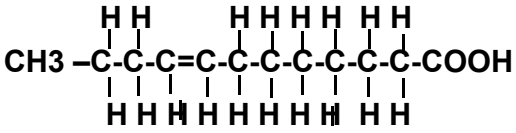
- R maybe
  - Choline
  - Inositol
  - Ethanolamine
  - Serine
  - Sphingomyelin

Simple lipids are

a) **Saturated (no double bonds)**
CH3 ----------COOH

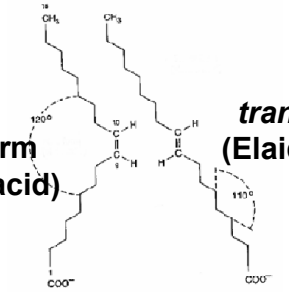
b) **Unsaturated (mono or poly double bonds)**
CH3 ----=---------- COOH
(Methyl (w) end Carboxyl end)

An unsaturated fatty acid (Omega 3)



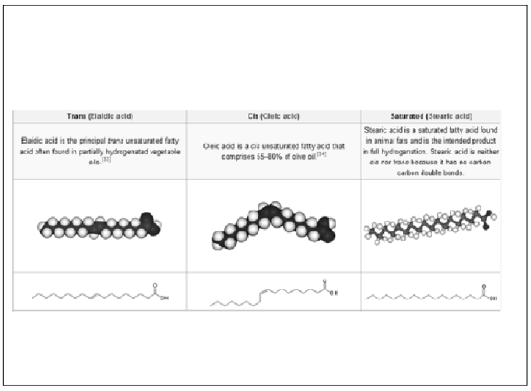
(Methyl (w) end Carboxyl end)

Unsaturated fatty acids can be in either *cis* or *trans* forms



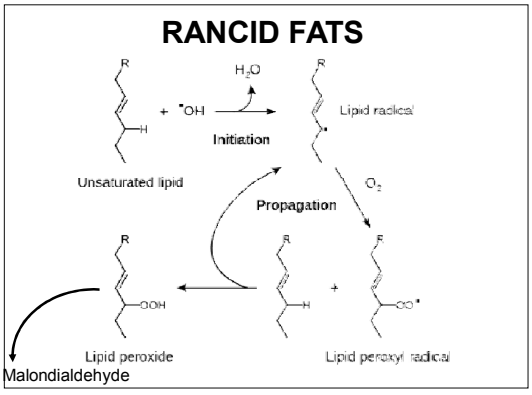
***cis* form (Oleic acid)**

***trans* form (Elaidic acid)**



Rancid Fats

- **Primarily occurs with unsaturated fats**
- **More susceptible to rancidity because of structure with many double bonds**
- **Fats turn rancid in the presence of free radicals or reactive oxygen species**



Rancid Fats

- Reactive oxygen species degrade polyunsaturated lipids forming malondialdehyde
- Reactive aldehyde causes toxic stress in cells and forms advanced lipoxidation end products
- Lead to loss of membrane integrity

Rancid Fats

- Malondialdehyde is used as a biomarker to assess the oxidative stress of a person
- It reacts with deoxyadenosine and deoxyguanosine in DNA to form DNA combinations which can be mutagenic

Rancid Fats

- Measure the oxidative stability of an oil
- Rancimat method measures the progress of the oxidation reaction
- Measures the volatile oxidation products, largely formic acid
- Biomarker Formic acid to test rancid oils

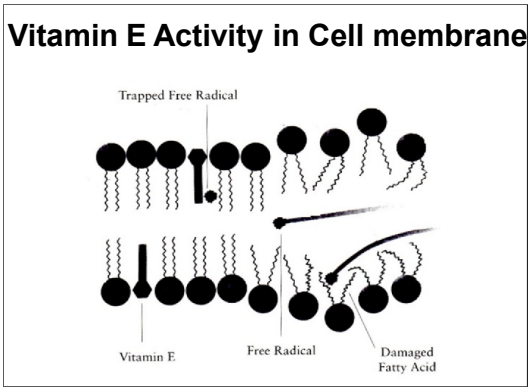
Rancid Fats

- To test if an oil or food is rancid
- Test patient with Formic acid to check not weakening in the clear
- Test oil or food with formic acid test vial on the body
- If SIM weakens, oil or food is rancid and contributing to lipid peroxidation

Rancid Fats

- To test if a person has lipid peroxidation:
- Test with Malondialdehyde
- If SIM weakens, cross check with oils from Product Kit 2
- Test for Smart Vitamin E, Smart Vitamin C to recycle

Vitamin E Activity in Cell membrane



Smart Vitamin E

- Organic Wheat germ oil
- Organic Pistachio nut oil
- Organic Sesame seed oil

Organic Wheatgerm Oil

- One of highest sources of Vitamin E - 150mg per 100g
- Tocopherols and tocotrienols
- Combination of enzymes, catalysts, plant compounds, minerals
- Synergy of natural components
- Optimal Vitamin E complex

Organic Pistachio Oil

- Excellent source of Vitamin E, 20mg per 100g
- Especially high in gamma tocopherol
- Contains polyphenol which have excellent anti-oxidant capability

Organic Sesame seed oil

- Sesamin – lignan compound
- Inhibits tocopherol-alpha-hydroxylation
- Causes a relative increase of Vitamin E in the body
- Gamma tocopherol and gamma tocotreinol

Epigenetics Plant Oils

- Cold pressed organic oils
- Not been chemically processed
- Steeped in watercress – enzyme phospholipase A & selenium
- Miron glass

Constitutional Oils

- RED – Flax, Hemp, Pumpkin, Olive Good mix of Omega 3, 6 & 9
- BLUE – Flax, Pumpkin, Walnut Greater proportion of Omega 3
- GREEN – Grape seed, Hazelnut, Peanut, Sesame Predominantly Omega 6

Epigenetics Culinary Oils

- **Flax seed oil**
- **Hemp seed oil**
- **Grape seed oil**
- **Hazelnut oil**
- **Walnut oil**
- **Pumpkin seed oil**
- **Olive oil**

Epigenetics Culinary Oils

- **Sesame seed oil**
- **Peanut oil**
- **Black Cumin seed oil**
- **Macadamia oil**
- **Wonder oil**
- **Smart oil**

High GLA content oils

- **Blackcurrant seed oil**
- **Evening Primrose oil**
- **Borage oil**

Fats and Oils in Dementia

- PUFAs used in brain DHA & AA
- DHA is primarily in cerebral cortex used for working memory and short term memory
- AA is primarily in hippocampus used for consolidation of short term to long term memory and spatial navigation

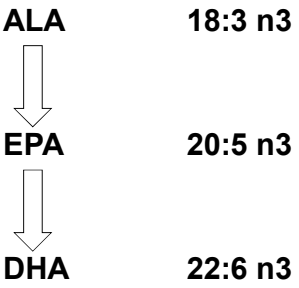
DHA Docosahexaenoic acid

- Most abundant omega 3 fatty acid
- 40% of PUFAs in brain
- 50% weight of neuron's membrane
- Synthesized from ALA
- Diet: Fish oil, breast milk

DHA

- Most unsaturated fatty acid in brain
- Structually comprises 22 carbons and 6 cis double bonds
- Greater tendency to oxidation
- Increases the fluidity of cell membranes

Synthesis of DHA



Enzymes in EFA conversion

- Desaturation – addition of a double bond
- Delta-6-desaturase
- Delta-5-desaturase
- Elongation – addition of 2 carbon atoms
- Elongase enzyme

Enzymes in EFA conversion

- Genetic variability in enzymes involved in fatty acid metabolism influence ability to generate LC PUFAs
- Polymorphisms in genes or acquired defect
- Look for the co-enzyme needed and mineral co-factors

Test for defects in DHA synthesis

- Ability to convert ALA to DHA
- Check if weaken to ALA
- May not show until taken an amount of ALA supplementation
- Negate weakness with co-enzymes, P5P, or co-factors, Zinc or Magnesium

DHA Dietary Sources

- Top fish sources:
  - Tuna, mackerel, swordfish, salmon, anchovies, herring, sardines, caviar
- Cooked salmon 500 – 1500 mg per 100g
- Recommended daily intake – 650 mg DHA plus EPA
- Algae based vegetable oils

Research on DHA and Dementia

- Low DHA associated with cognitive decline
- Likely to develop dementia and other cognitive disorders
- Study in Canada – Alzheimer's patients had lower DHA level

Research on DHA and Dementia

- DHA accumulates in phosphotidylserine (PS)
- PS controls apoptosis and low DHA levels lower neural cell PS and increases neural cell death
- Particularly in hippocampus associated with memory consolidation

DHA and Alzheimer's

- Sufferers have much lower levels in neurons of hippocampus
- Hippocampus is severely affected in Alzheimer's – working memory
- DHA supplementation improves memory in Alzheimer's and age related memory loss

DHA and Alzheimer's

- Studies in mice and primates show DHA depleted diets impair learning and memory
- Re-feeding DHA diet reverses these impairments
- Chicago and Rotterdam studies found a 60% reduction in Alzheimer's taking omega 3 oils

DHA and Alzheimer's

- Also found that intake of plant derived omega 3 ALA was associated with a reduction in risk of Alzheimer's in subjects with APOE4
- APOE4 is a powerful indicator of Alzheimer's

Conversion of fatty acids to DHA

- LNA not converted to DHA efficiently in humans
- LNA elongated, desaturated, transported to and from peroxisomes and then shortened from 24:6 to 22:6
- Estimated that 10-40g of flax seed oil to produce 200 mg per day

Clinical Research into DHA

- Marine algae very expensive
- Deficiency in DHA caused by conversion problems
- Combination of 2 oils consistently strengthens cases of DHA deficiency
- Assumption that these 2 oils allow patient to make own DHA

Smart Omega 3

- Combination of Pumpkin seed oil and Rapeseed oil, Vitamin E
- Rapeseed oil – unrefined, organic, cold pressed, GM free
- Ratio 3:1
- Lloyd Horrocks study at Ohio State University into rapeseed oil and production of DHA

Smart Omega 3

- "LNA must have been channelled into DHA synthesis, perhaps by inhibition of the delta-6-desaturase decreasing conversion of LA to ARA"
- Some factors in Pumpkin seed oil inhibit LA converting to ARA and stimulate LNA to DHA conversion

Summary of DHA benefits

- Crucial for healthy structure and function of brain
- Essential for the adult brain where it impacts brain structure and signalling system
- Promotes nervous system development and optimal memory
- Helps prevent age related memory decline & Alzheimer

Arachidonic Acid (AA)

- Neurological health is dependent on sufficient quantities of AA
- Omega 6 fatty acid, from LA
- Maintains the hippocampal cell membrane fluidity
- Protects brain from oxidative stress
- Dietary source meat, eggs, dairy

Arachidonic Acid (AA)

- Activates syntaxin-3, a protein involved in growth & repair of neurons
- Involved in early neurological development
- In adults the disturbed metabolism contributes to Alzheimer's and dementia

Foods high in AA

- Red meat – beef, lamb, veal, venison, organ meats
- Poultry
- Pork – pork loin in particular
- Oils – peanut, sesame, olive, avocado
- Egg yolks

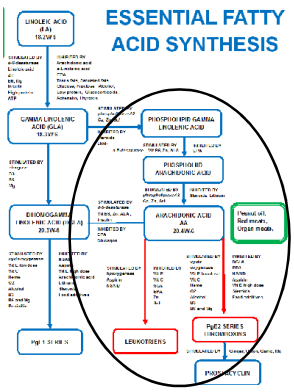
Synthesis of AA

LA	18:2 n-6
⇩	
GLA	18:3 n-6
⇩	
DGLA	20:3 n-6
⇩	
AA	20:4 n-6

Test for defects in AA synthesis

- Main blockage tends to be between LA and GLA, delta-6-desaturase enzyme, P5P, Zinc, Magnesium
- Pathway affected if have blockages in other parts of EFA synthesis
- Dietary factors – trans fats, saturated fats, glucose, alcohol
- Hormonal imbalances – adrenalin, thyroxin, glucocorticoids

AA as the Bad Guy



AA as the Bad Guy

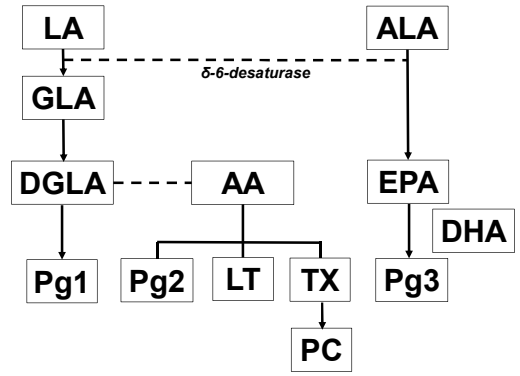
- Key inflammatory intermediate
- AA is metabolised to both proinflammatory and anti-inflammatory molecules
- Keep Inflammatory process under control, balance of hormones
- Continual low level inflammation destroys organs including brain

AA as the Bad Guy

- Remove building blocks of excess
- Reduce intake of bad omega 6 fats, trans & hydrogenated fats
- Keep insulin levels low and stable
- Nutrients from chart
- Introduce ginger, onion, garlic (GOG) into diet

FATS in the Prevention of Memory Loss and Dementia

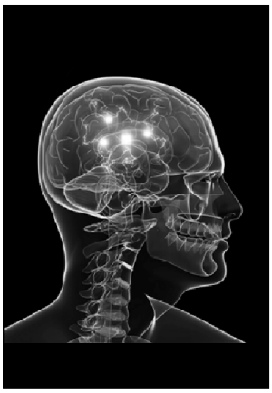
- Maintain a good supply high quality, cold pressed parent essential oils
- ORGANIC is paramount – toxins cause of neurological decline
- Guard against rancid fats and lipid peroxidation
- Check levels of DHA & AA and fatty acid synthesis

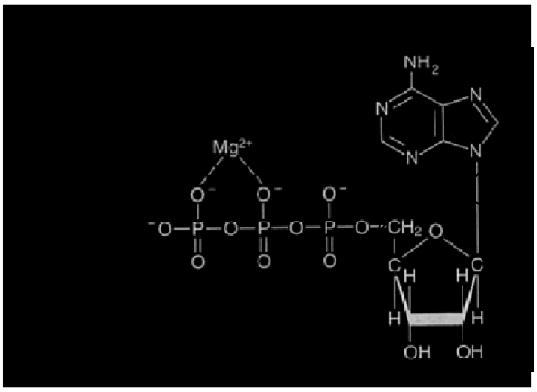


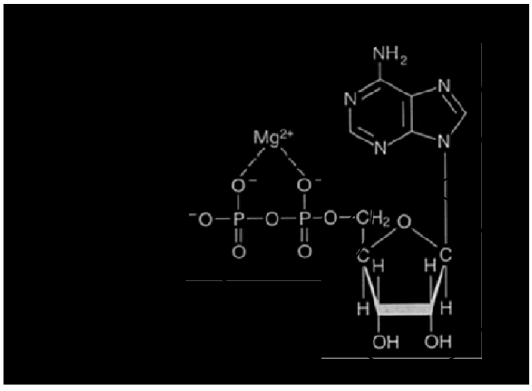
Key nutrients for synthesising the phospholipids

Acetyl CoA (Vit B5, Magnesium, P5P)
NAD, NADPH (Vit B3 complex)
Mg, Zn, SAM (Mg, P-5-P, Folates, B12)
Choline
Serine
Inositol
Saturated fatty acids C16-18
Unsaturated fatty acids C18-24
Lecithin

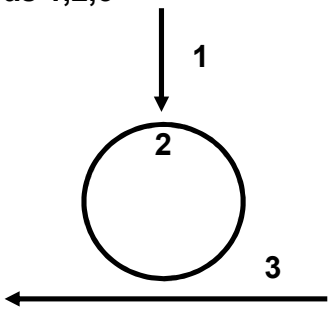
The brain is 2% of the weight of the body but uses 20% of all ATP produced.

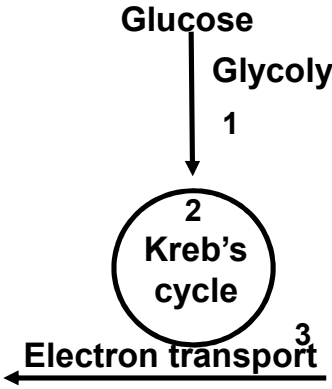






Understanding energy production is as easy as 1,2,3



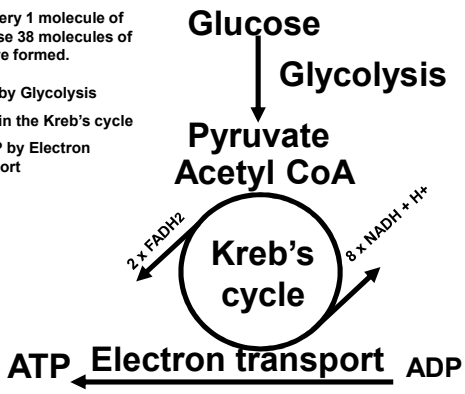


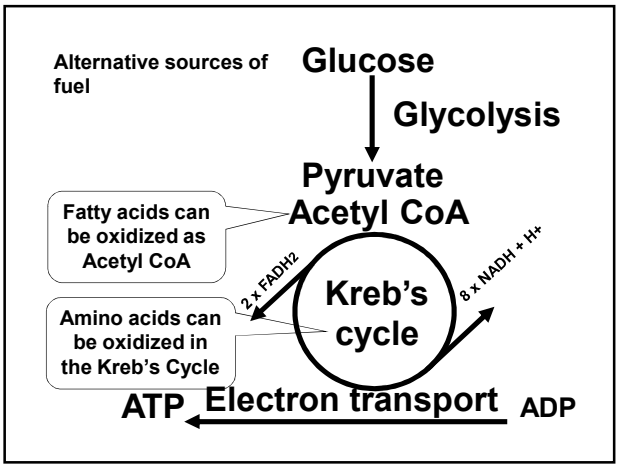
For every 1 molecule of Glucose 38 molecules of ATP are formed.

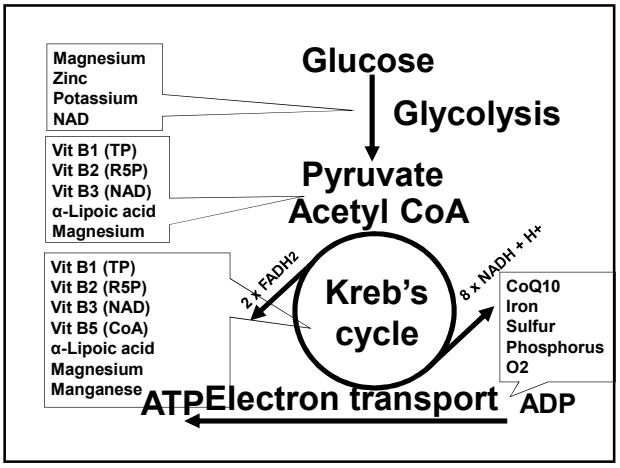
8 ATP by Glycolysis

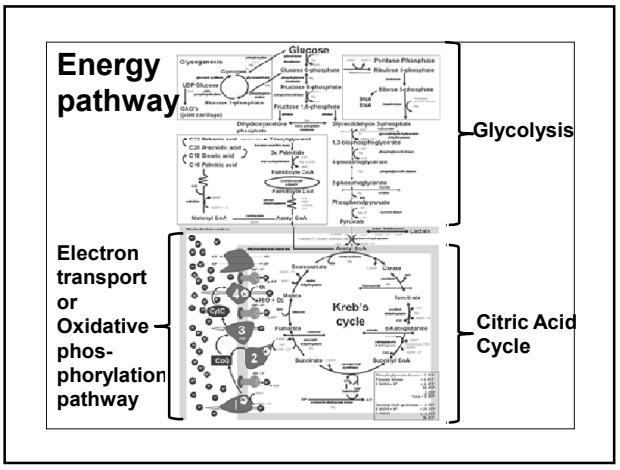
2 ATP in the Kreb's cycle

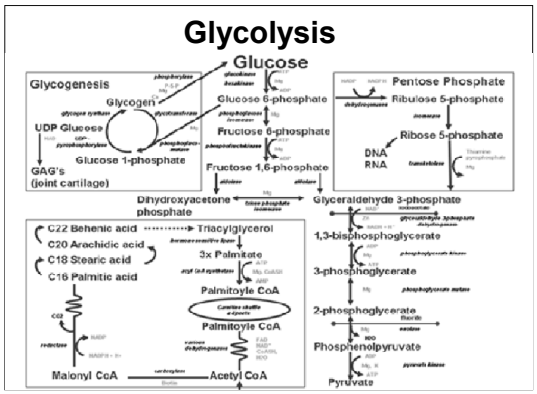
28 ATP by Electron transport

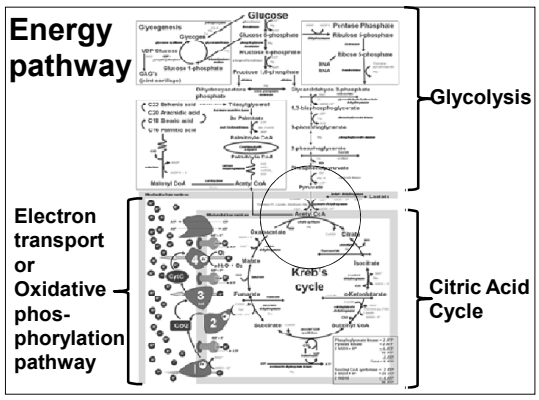


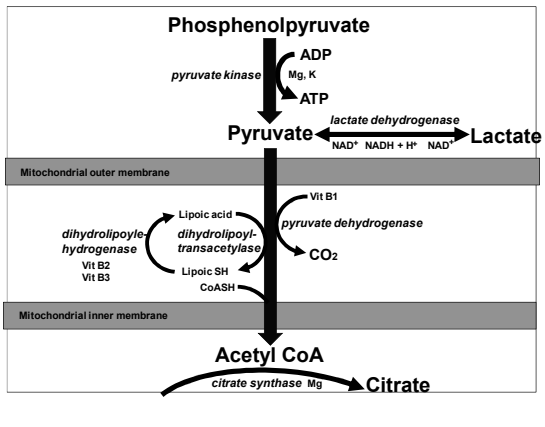

Alternative sources of fuel
Glucose
Glycolysis
Pyruvate
Acetyl CoA
Fatty acids can be oxidized as Acetyl CoA
Amino acids can be oxidized in the Kreb's Cycle
2 x FADH2
Kreb's cycle
8 x NADH + H+
ATP
Electron transport
ADP


Magnesium
Zinc
Potassium
NAD
Glucose
Glycolysis
Vit B1 (TP)
Vit B2 (R5P)
Vit B3 (NAD)
α-Lipoic acid
Magnesium
Pyruvate
Acetyl CoA
Vit B1 (TP)
Vit B2 (R5P)
Vit B3 (NAD)
Vit B5 (CoA)
α-Lipoic acid
Magnesium
Manganese
2 x FADH2
Kreb's cycle
8 x NADH + H+
CoQ10
Iron
Sulfur
Phosphorus
O2
ATP
Electron transport
ADP

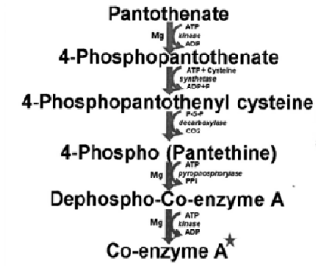

Energy pathway
Glucose
Glycolysis
Electron transport or Oxidative phos-phorylation pathway
Kreb's cycle
Citric Acid Cycle


Glycolysis
Glucose
Glycogenesis
Glycogen
UDP Glucose
Glucose 1-phosphate
GAG's
(joint cartilage)
Glucose 6-phosphate
Fructose 6-phosphate
Fructose 1,6-phosphate
Pentose Phosphate
Ribulose 5-phosphate
Ribose 5-phosphate
DNA
RNA
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
1,3-bisphosphoglycerate
3-phosphoglycerate
2-phosphoglycerate
Phosphenolpyruvate
Pyruvate
C22 Behenic acid
C20 Arachidic acid
C18 Stearic acid
C16 Palmitic acid
Triacylglycerol
3x Palmitate
Palmitoyle CoA
Palmitoyle CoA
Malonyl CoA
Acetyl CoA

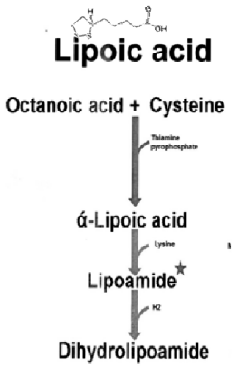

Energy pathway
Glycolysis
Electron transport or Oxidative phos-phorylation pathway
Citric Acid Cycle
Krebs cycle

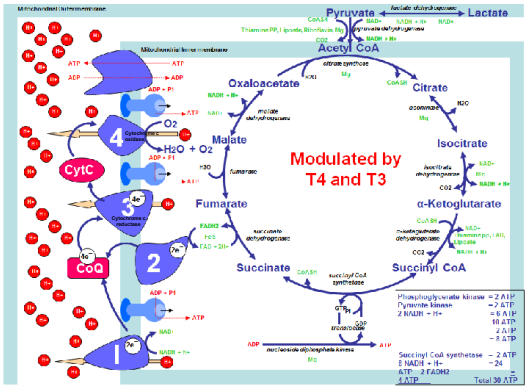

Phosphenolpyruvate
pyruvate kinase
ADP
Mg, K
ATP
Pyruvate
lactate dehydrogenase
NAD+ NADH + H+ NAD+
Lactate
Mitochondrial outer membrane
Vit B1
Lipoic acid
dihydrolipoyle hydrogenase
Vit B2
Vit B3
dihydrolipoyl-transacetylase
pyruvate dehydrogenase
CO2
Lipoic SH
CoASH
Mitochondrial inner membrane
Acetyl CoA
citrate synthase Mg
Citrate

Vitamin B5

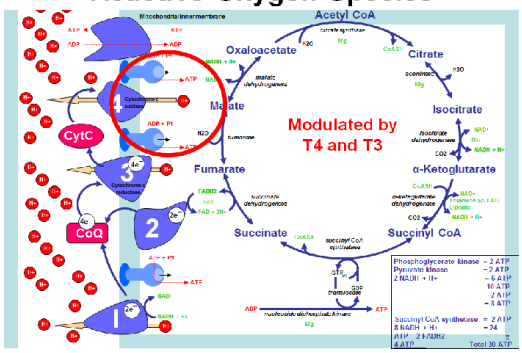


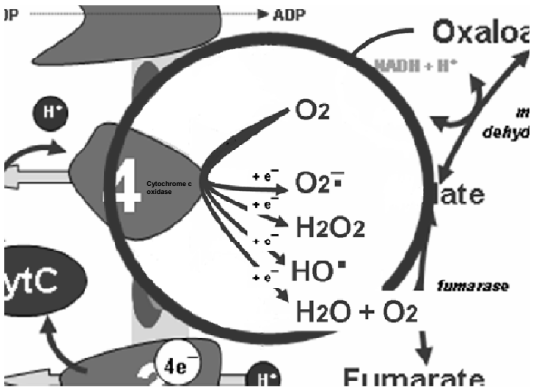
Alpha Lipoic Acid catalyses the conversion of Pyruvate to Acetyl CoA and the conversion of alpha Keto-glutarate to Succinyl CoA



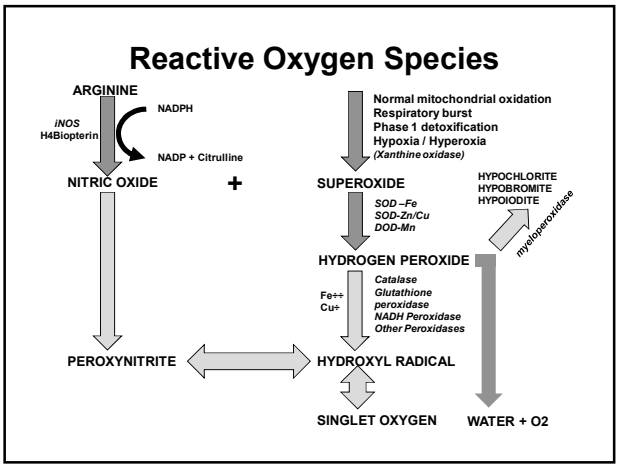


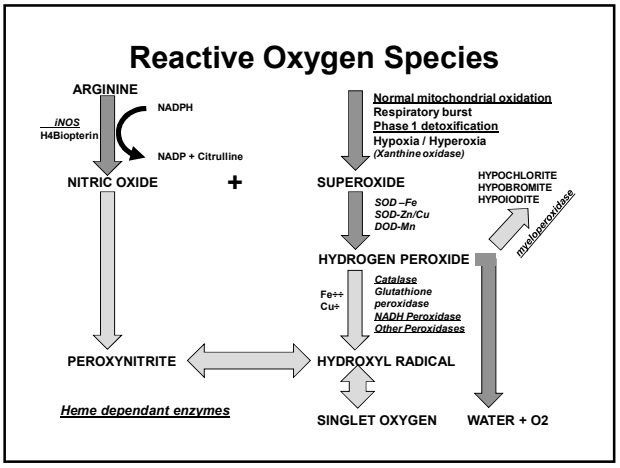
Reactive Oxygen Species





Reactive Oxygen Species (ROS)


Reactive Oxygen Species
ARGININE
iNOS
H4Biopterin
NADPH
NADP + Citrulline
NITRIC OXIDE
+
SUPEROXIDE
Normal mitochondrial oxidation
Respiratory burst
Phase 1 detoxification
Hypoxia / Hyperoxia
(Xanthine oxidase)
HYPOCHLORITE
HYPOBROMITE
HYPOIODITE
myeloperoxidase
SOD –Fe
SOD-Zn/Cu
DOD-Mn
HYDROGEN PEROXIDE
Fe++
Cu+
Catalase
Glutathione peroxidase
NADH Peroxidase
Other Peroxidases
PEROXYNITRITE
HYDROXYL RADICAL
SINGLET OXYGEN
WATER + O2


Reactive Oxygen Species
ARGININE
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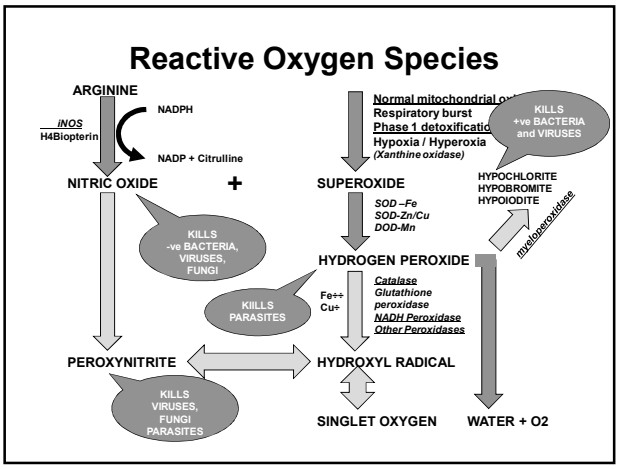
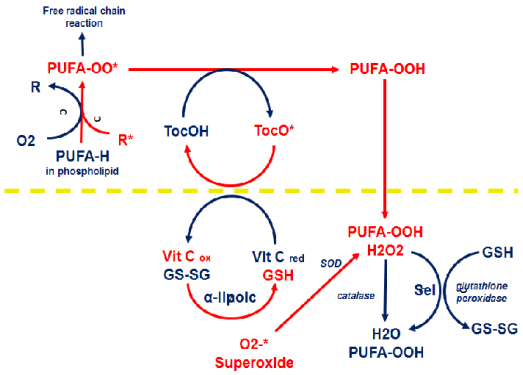
+
SUPEROXIDE
Normal mitochondrial oxidation
Respiratory burst
Phase 1 detoxification
Hypoxia / Hyperoxia
(Xanthine oxidase)
HYPOCHLORITE
HYPOBROMITE
HYPOIODITE
myeloperoxidase
SOD –Fe
SOD-Zn/Cu
DOD-Mn
HYDROGEN PEROXIDE
Fe++
Cu+
Catalase
Glutathione peroxidase
NADH Peroxidase
Other Peroxidases
PEROXYNITRITE
HYDROXYL RADICAL
SINGLET OXYGEN
WATER + O2
Heme dependant enzymes


Reactive Oxygen Species
ARGININE
iNOS
H4Biopterin
NADPH
NADP + Citrulline
NITRIC OXIDE
+
SUPEROXIDE
Respiratory burst
Phase 1 detoxificatio
Hypoxia / Hyperoxia
(Xanthine oxidase)
KILLS
+ve BACTERIA
and VIRUSES
HYPOCHLORITE
HYPOBROMITE
HYPOIODITE
myeloperoxidase
SOD –Fe
SOD-Zn/Cu
DOD-Mn
KILLS
-ve BACTERIA,
VIRUSES,
FUNGI
HYDROGEN PEROXIDE
KIILLS
PARASITES
Fe++
Cu+
Catalase
Glutathione peroxidase
NADH Peroxidase
Other Peroxidases
PEROXYNITRITE
HYDROXYL RADICAL
KILLS
VIRUSES,
FUNGI
PARASITES
SINGLET OXYGEN
WATER + O2

Calorie restriction, Turmeric and the Keto-genic diet create less Reactive Oxygen Species (ROS).

Anything that upregulates inflammation will lead to brain degeneration.



Vitamin E
the phospholipids of the mitochondria, endoplasmic reticulum and the plasma membranes possess affinities for tocopherols and the vitamin appears to concentrate predominantly at these sites.

Mitochondria

In addition to supplying cellular energy, mitochondria are involved in other tasks such as signalling, cellular differentiation, cell death, as well as maintaining the control of the cell cycle and cell growth.

Mitochondrial compartments include the outer membrane, the intermembrane space, the inner membrane, and the cristae and matrix.
A mitochondrion contains outer and inner membranes composed of phospholipid bilayers and proteins. The two membranes have different properties.

Disruption of the outer membrane permits proteins in the intermembrane space to leak into the cytosol, leading to certain cell death.

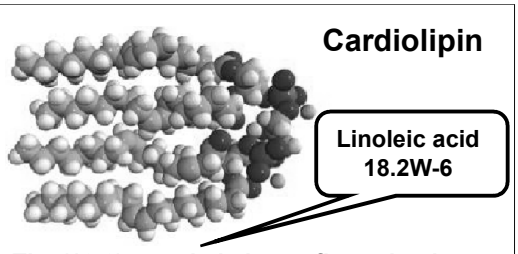
The inner mitochondrial membrane contains proteins with five types of functions:
1. Those that perform the redox reactions of oxidative phosphorylation
2. ATP synthase, which generates ATP in the matrix

3. Specific transport proteins that regulate metabolite passage into and out of the matrix
4. Protein import machinery.
5. Mitochondria fusion and fission protein.

It has a very high protein-to-phospholipid ratio which is about 1 protein for 15 phospholipids.

It is rich in the phospholipid, cardiolipin. Cardiolipin contains four fatty acids rather than two, and helps to make the inner membrane impermeable.
Cardiolipin contains 18-carbon fatty alkyl chains with 2 unsaturated bonds on each of them. (e.g. Linoleic acid).

Cardiolipin



The (18:2) 4 acyl chain configuration is an important structural requirement for the high affinity of CL to inner membrane proteins in mammalian mitochondria.

Cardiolipin appears to be stimulated by Turmeric.

The inner mitochondrial membrane is compartmentalized into numerous cristae, which expand the surface area of the inner mitochondrial membrane, enhancing its ability to produce ATP.

One recent mathematical modeling study has suggested that the optical properties of the cristae in filamentous mitochondria may affect the generation and propagation of light within the tissue.

Thar, R.; Kühl, Michael (2004). "Propagation of electromagetic radiation in mitochondria?" (PDF). J Theor Biol 230 (2): 261–270

Energy equates with Health and with Life.
When ATP is made in the mitochondria photons known as biophotons of low luminosity are emitted from the various cytochrome molecules.
It is thought that such biophotons are carriers of information.

These biophotons should be of a broad spectrum, so called white light.
Emissions of other monochromic biophotons of specific wavelength colours would indicate an energy system out of homeostasis.
For example *cytochrome p450* emits at this wavelength in the presence of carbon monoxide.

The matrix is the space enclosed by the inner membrane. It contains about 2/3 of the total protein in a mitochondrion.
The matrix is important in the production of ATP with the aid of the ATP synthase contained in the inner membrane.

The matrix contains a highly concentrated mixture of hundreds of enzymes, special mitochondrial ribosomes, tRNA, and several copies of the mitochondrial DNA genome.
Of the enzymes, the major functions include oxidation of pyruvate and fatty acids, and the citric acid cycle.

Mitochondria have their own genetic material, and the machinery to manufacture their own RNAs and proteins.
A published human mitochondrial DNA sequence revealed 16,569 base pairs encoding 37 total genes: 22 tRNA, 2 rRNA, and 13 peptide / protein genes.

A transfer RNA (abbreviated tRNA) is an adaptor molecule composed of RNA, typically 76 to 90 nucleotides in length, that serves as the physical link between the nucleotide sequence of nucleic acids (DNA and RNA) and the amino acid sequence of proteins. It does this by carrying an amino acid to the protein synthetic machinery of a cell (ribosome) as directed by a three-nucleotide sequence (codon) in a messenger RNA (mRNA). As such, tRNAs are a necessary component of protein translation, the biological synthesis of new proteins according to the genetic code.

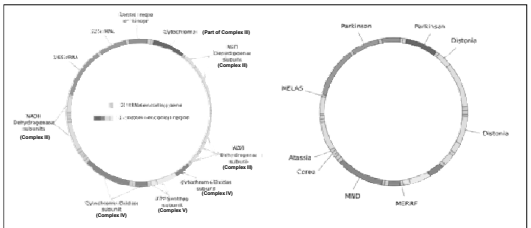
Mitochondrial.DNA (mtDNA) is the DNA located in mitochondria. It is inherited solely from the mother.
mtDNA is organized as a circular, covalently closed, double-stranded DNA.
100-10,000 separate copies of mtDNA are usually present per cell.

The two strands of mtDNA are differentiated by their nucleotide content, with a guanine-rich heavy strand and a cytosine-rich light strand.
The heavy strand encodes 28 genes, and the light strand encodes 9 genes for a total of 37 genes.

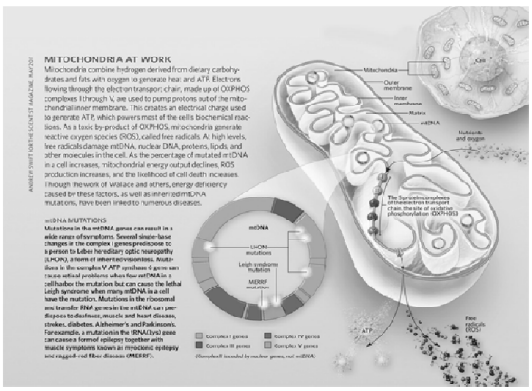
Mitochondrial DNA is replicated by the DNA polymerase gamma complex – a zinc dependant enzyme.
mtDNA is particularly susceptible to reactive oxygen species generated by the respiratory chain due to its proximity.

Though mtDNA is packaged by proteins and harbours significant DNA repair capacity, these protective functions are less robust than those operating on nuclear DNA and are therefore thought to contribute to enhanced susceptibility of mtDNA to oxidative damage.

The outcome of mutation in mtDNA may be alteration in the coding instructions for some proteins, which may have an effect on organism metabolism and/or fitness.
Evidence suggests that they might be major contributors to the aging process and age-associated pathologies.



Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes – abbreviated to MELAS – is one of the family of mitochondrial cytopathies, which also include MERRF, (Myoclonic Epilepsy with Ragged Red Fibres) and Leber's hereditary optic neuropathy.



Mutations in mtDNA upset a careful balance of reactive oxygen species (ROS) production and enzymatic ROS scavenging (by enzymes like superoxide dismutase, catalase, glutathione peroxidase and others).

As mitochondrial DNA accumulates genetic damage caused by free radicals, the mitochondria lose function and leak free radicals into the cytosol. A decrease in mitochondrial function reduces overall metabolic efficiency..

Mitochondrial Complexes

Complex I
NADH dehydrogenase (ubiquinone) **is an enzyme of the respiratory chain and catalyzes the transfer of electrons from NADH to coenzyme Q10 and it is located in the.inner mitochondrial membrane.**

It is one of the "entry enzymes" of cellular respiration or oxidative phosphorylation in the mitochondria.

The reaction of complex I is:
$NADH + H^+ + CoQ + 4H^+_{in} \rightarrow NAD^+ + CoQH_2 + 4H^+_{out}$

Recent investigations suggest that complex I is a potent source of reactive oxygen species. Complex I can produce superoxide (as well as hydrogen peroxide), through at least two different pathways.

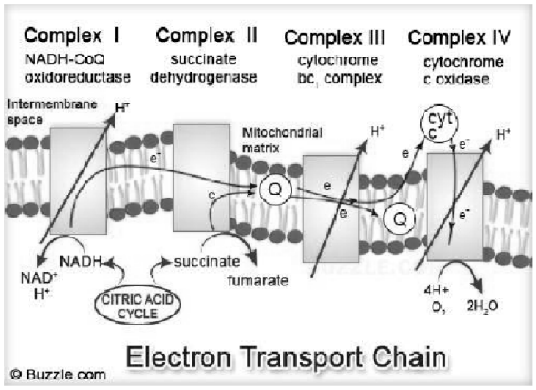
During reverse electron transfer, complex I might be the most important site of superoxide production within mitochondria, with up to 5% of electrons being diverted to superoxide formation.

It can be a very potent source of superoxide.when succinate concentrations are high and oxaloacetate or malate concentrations are low.

Pesticides destroy the mitochondria.
Exposure to pesticides can inhibit Complex I and cause disease symptoms. Chronic exposure to low levels of dichlorvos, an organophosphate used as a pesticide, has been shown to cause liver dysfunction.

This occurs because dichlorvos alters Complex I and II activity levels, which leads to decreased mitochondrial electron transfer activities and decreased ATP synthesis.

Complex II *Succinate.dehydrogenase or succinate-coenzyme Q reductase* is an enzyme complex, bound to the inner mitochondrial membrane. It is the only enzyme that participates in both the citric acid cycle and the electron transport chain.



In citric acid cycle it catalyzes the oxidation of succinate to fumarate with the reduction of ubiquinone to ubiquinol. This occurs in the inner.mitochondrial membrane by coupling the two reactions together..

Complex III
***Coenzyme Q : cytochrome c — oxidoreductase* is the third complex in the electron transport chain, playing a critical role in biochemical generation of ATP (oxidative phosphorylation). The cytochrome b subunit contain two heme molecules and the cytochrome c contains one heme.**

Mutations in Complex III cause exercise intolerance as well as multisystem disorders.

A small fraction of electrons leave the electron transport chain before reaching complex IV. Premature electron leakage to oxygen results in the formation of superoxide.

Complex IV
***Cytochrome c oxidase* is a large transmembrane protein. It receives an electron from each of four cytochrome c molecules, and transfers them to one oxygen molecule, converting molecular oxygen to two molecules of water.**

In the process, it binds four protons from the inner aqueous phase to make water, and in addition translocates four protons across the membrane, helping to establish a transmembrane difference of proton electrochemical potential that the *ATP synthase* then uses to synthesize ATP.

The complex contains two hemes, (cytochrome a and cytochrome a_3), and two copper centres, the Cu_A and Cu_B centres.

Cytochrome c oxidase is encoded by mitochondrial DNA.

Cyanide, sulfide, azide, and carbon monoxide all bind to cytochrome c oxidase, thus competitively inhibiting the protein from functioning, which results in chemical asphyxiation of cells. Methanol converted into formic acid, also inhibits the same oxidase system.

Complex IV – cytochrome c oxidase is protected and stimulated by - SMART Vitamin E

Light at 660 nm, 830 nm and 840 nm (peaks of cytochrome C oxidase absorption)

Mitochondrial function

There are on average 1500 mitochondria in every body cell with the exception of the red blood cells. In heart muscle cells they average 2000 and in nerve cells up to 5000. In the heart, mitochondria account for 70% of its weight. When mitochondria cannot work normally, the production of energy is by mitochondria is disrupted.

The energy ATP is no longer produced with the assistance of oxygen but outside the mitochondria in the cytoplasm and without oxygen by glycolysis or in less serious disruptions with oxygen but without the production of oxygen radicals.

In the process the differentiated cell performances of all organelle systems are no longer maintained but instead the cell division cycle is activated.
The word "Mitochondria" comes from the Greek *mitos* meaning thread and *chondros* meaning grain.

90% of the oxygen we inhale is required in mitochondria for the modulation of energy. This form of energy production within the mitochondria is termed "high performance energy". This energy is not only heat energy but more importantly *information energy* with driving functions.

In the "high performance model" reactive oxygen radicals are always and unavoidably formed which can damage potential cells and mitochondria. If they are not neutralized, cell or mitochondria membrane components or genetic fragments could be damaged or destroyed.

Free radicals like oxygen and NO gas play an important role in the defence against tumour cells and pathogens, proliferating within cells and is a completely normal physiological process.
Sulfur compounds are decisive for neutralizing these radicals such as reduced glutathione and sulfur containing foods.

If in the production of mitochondrial energy the accumulating oxygen radicals or industrial toxins can no longer be quenched, they can potentially cause serious damage at a cellular level. In order to protect themselves from this the mitochondria reduce their activities.

In doing so there are fewer oxygen radicals produced but the consequence is a drop in system cell performance. Dr Kremer called this process the "protective switch". Here the energy production is switched from the mitochondria to the cytoplasm.

From an evolutionary biological viewpoint the older cell division program governed by the anaerobic archaeal portion of the partnership is activated utilizing blood sugar which activates cell division.

The endosymbiotic relationship of mitochondria with their host cells was popularized by Lynn Margulis. The endosymbiotic hypothesis suggests that mitochondria descended from bacteria that somehow survived endocytosis by another cell, and became incorporated into the cytoplasm.

Three domains of kingdom of Life

1. **Archaea – single celled organisms lacking nuclei.**
2. **Bacteria – also lacking nuclei**
3. **Eukarya – contain nuclei (single cell protists, multi cellular algae, fungi, plants, animals and humans).**

All Eukarya, including humans owe their existence to a unique act of fusion in evolution, namely the colonization of a voluminous type of Archaea as a host / stem cell by single cellular organisms from the bacteria domain. This intracellular symbiosis from members of different domains took place 2.1 billion years ago.

This was the time when the earth's atmosphere was changing from methane to oxygen. Before the Ice age of 4.5 billion years ago the atmosphere was dominated by methane and carbon dioxide. CH_4 was produced by the anaerobic Archaea which convert CO_2 to CH_4 and CO_2 was due to volcanic activities.

After the melting of the ice the O_2 concentration rose while methane concentrations fell exponentially. Cell symbiosis took place at exactly the point in time these two atmospheric gas curves intersected allowing certain Archaea to become facultative aerobes to produce ATP.

ATP metabolism has been demonstrated by microbiologists in methane producing Archaea and bacteria. In oxygen free milieus these archaea can survive by switching ATP production to glycolysis.

Polyphenols cannot be synthesised by mammals which is why they have characteristics of vitamins. They are essential for intact mitochondrial function, systemic diseases and premature aging.

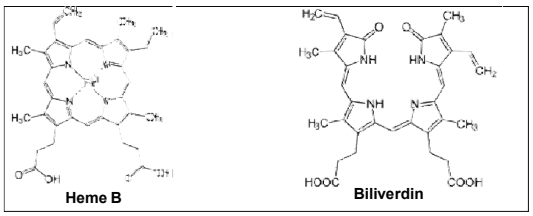
If the electron flow in Complex 4 of the respiratory chain to O2 is permanently disturbed then a failure in the modulation of ATP occurs and increasing numbers of oxygen and other radicals form that can attack and damage the macromolecules (nucleic acids, proteins, lipids).

In order to prevent this danger the key enzyme *hemeoxygenase* up-regulates. The enzyme uses O2 as co-factor for the production of carbon monoxide (CO).

***Hemeoxygenase* is an enzyme that catalyzes the degradation of heme. This produces biliverdin, iron, and carbon monoxide. It cleaves the heme ring at the alpha-methene bridge to form either biliverdin or, if the heme is still attached to a globin, verdoglobin.**

Biliverdin is subsequently converted to bilirubin by biliverdin reductase.

$$\text{Heme b} + 3O_2 + 3\tfrac{1}{2}\text{NADPH} + 3\tfrac{1}{2}H^+ \rightarrow \text{biliverdin} + Fe^{2+} + CO + 3\tfrac{1}{2}NADP^+ + 3H_2O$$



Heme B

Biliverdin

This reaction can occur in virtually every cell; the classic example is the formation of a bruise, which goes through different colours as it gradually heals: red heme to green biliverdin to yellow bilirubin. Under normal conditions, the activity of *heme oxygenase* is highest in the spleen, where old erythrocytes are sequestrated and destroyed.

When O2 is deficient the even more effective cyanide gas (CN^-) is formed instead of CO. CN^- is in humans the strongest mitochondrial respiratory poison.

Curcumin effectively inhibits nearly all signal paths. The actions of curcumin can be explained by the fact that curcumin in the violet spectral range of visible light absorbs with nearly the same wavelength - 430mm- as the electron transforming molecule cytochrome c that is more rapidly

broken up by the protective enzyme heme oxygenase. Curcumin, bridges the III and IV complex photon switch "short circuit" of the respiratory chain in mitochondria and thus normalizes the information transfer for maintaining modulation of ATP.

There is a broad spectrum of classes of substances responding to natural light.

NB. Use only Organic Turmeric as non – organic contains pesticides that inhibit the mitochondrial respiratory chain.
e.g. Pyrethroids, Carbendazim

Dementia

Dementia is a broad category of brain diseases that cause a long term and often gradual decrease in the ability to think and remember such that a person's daily functioning is affected. Other common symptoms include emotional problems, problems with language, and a decrease in motivation.

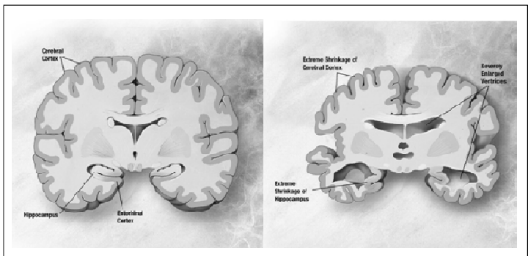
The most common type of dementia is
1. Alzheimer's disease which makes up 50% to 70% of cases.
2.Vascular.dementia(25%),
3. Lewy body dementia (15%), 4. Fronto-temporal dementia

Less common causes include
5. Normal pressure hydrocephalus
6. Parkinson disease
7. Syphilis
8. Creutzfeldt–Jakob disease

Causes
Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which have an onset before age 65.

Between 40 and 80% of people with AD possess at least one APOE4 allele.

Causes
Head injuries increase risk
Oxidative stress and Inflammation
Insulin resistance
Microbiome
Nutritional imbalances
Allergy / Intolerances
Methylation defects
Toxicity especially Mercury and DDT



Comparison of a normal aged brain (left) and the brain of a person with Alzheimer's (right).

The *tau hypothesis* proposes that tau protein abnormalities initiate the disease cascade. In this.model, hyperphosphorylated tau begins to pair with other threads of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies.

When this occurs, the microtubules disintegrate, destroying the structure of the cell's cytoskeleton which collapses the neuron's transport system (can be the effect of mercury toxicity).This may result in malfunctions in biochemical communication between neurons and later in the death of the cells.

High education decreases the risk. Researchers in California have shown that most 90 year olds do not have dementia.

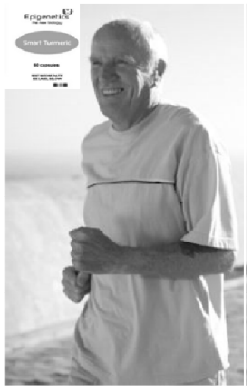
Alzheimer's degenerative changes begin in the hippocampus which starts to shrink so short bterm memory is affected first.
The brain losses its plasticity and its ability to make connections between neurones, many of which will die.

Decline occurs because of
1. **Learned Non – Use**
2. **Noisy brain or brain dysrhythmia**
3. **Absence of Rapid formation of neuronal assemblies. Every mental act creates different networks.**

The most impressive protection from cognitive decline was from
1. **Exercise – walking 2 miles a day or bicycling 10 miles a day.**
2. **Healthy diet – 5 a day+**
3. **Normal body weight BMI 18-25**
4. **Low alcohol**
5. **No smoking**

Walking reduces the risk of dementia by 60% - research showed this at Cardiff University – followed several thousand men between ages 40 and 59 testing them every 5 years for 30 years.

Aerobic exercise and Turmeric are epigenetic modulators of brain neurogenesis.



Exercise stimulates the production of
Glial Derived Neurotrophic Factor (GDNF)
Brain Derived Neurotrophic Factor (BDNF)
Which stimulate new brain cells and connections.

Increased running and environmental enrichment reduces the loss of acetylcholine and dopamine cells.
Smaller stresses prepare the body for greater stress and stimulate growth such as walking fast and breaking a sweat.
Continuous stress leads to neuronal loss.

Most growth is in the hippocampus that turns short term memory into long term memory and in the basal ganglia especially the striatum.

Exercise increases learning proportional to the rise in BDNF.
A combination of learning and exercise maintains brain plasticity.

Learning turns on genes that express more BDNF and BDNF facilitates learning.
<u>The more you learn the better you become at learning.</u>
A sedentary lifestyle is a significant risk factor to memory loss, heart disease, cancer and diabetes.

Exercise becomes more important as we age – not less.

Learned non-use occurs due to lack of stimulation and exercise.
This is seen in people who have strokes.
People learn not to use bits of their brain that don't work.
Exercise stops a newly injured system from going down.

Exercise should be one of the first recommendations made with a person with early signs of Alzheimer's disease.
The worst thing is to decrease activity.
Strength training, stretching and coordinated movement exercises are the most important.

Walking 3x a week for 45 minutes each time is the goal.
Start with 10 minutes 3x a week for the first 2 weeks.
Increase by 10 minutes every 2 weeks.

APOE4

A specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. Whilst apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain.

Apolipoprotein E (APO-E) is a plasma lipoprotein which plays a basic role in the degradation of particles rich in cholesterol and triglycerides. It is able to bind to LDL receptors, but also to receptors for chylomicron remnants. There are three major APO-E isoforms, E2, E3, and E4.

Their role in lipoprotein metabolism is related to their affinity for receptors. Allele E3 is 60% population and APO-E3 affects metabolism of lipoproteins in a standard way. Allele E2 (contains cysteine) is associated with lower LDL levels, whereas allele E4 with higher LDL levels.

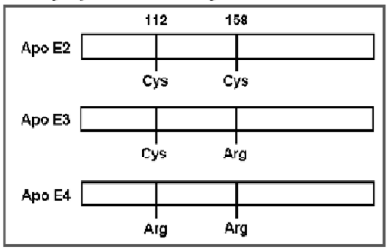
This has an impact on the progression of atherosclerosis. Allele E2 exhibits a protective role, whereas allele E4 is associated with a high risk factor. Lipoprotein(a) is a plasma lipoprotein, consisting of apolipoprotein(B), linked by a covalent bond with the LDL particle.

Boyd Haley, a University of Kentucky biochemist who researches heavy-metal neurotoxicology, explains that APO-E—a protein crucial in carrying mercury out of the body—comes in three varieties, ranging from one that can carry out two atoms of mercury for

every molecule of APO-E, to the least protective version, APO-E4, which doesn't carry out any. Both autistics and Alzheimer's patients tend to have APO-E4. "There is clearly a subpopulation of people who can't excrete even low levels of mercury effectively," says Haley.

APO –E2 contains two sulfhydryls from cysteine that can combine heavy metals such as mercury that APO-4 lacks. In APO-E3 one of the sulfhydryls is replaced by arginine amd in APO-E4 both sulfhydryls are replaced by arginine. The second highest level of APO proteins is in the CSF.

Substitution of Arginine for Cysteine in Apo E3 and Apo E4 at Positions 112 and 158 Results in Loss of Potential Binding Sites for Sulfhydryl Reactive Heavy Metals such as Mercury



ALT Affinity Labeling Technologies, Inc. 1999

APO E4 enhances amyloid (beta) production, high insulin levels.

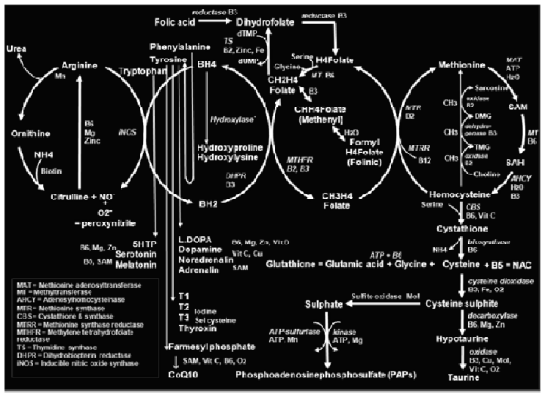
Antioxidants help protect against oxidative stress created by metal toxicity.

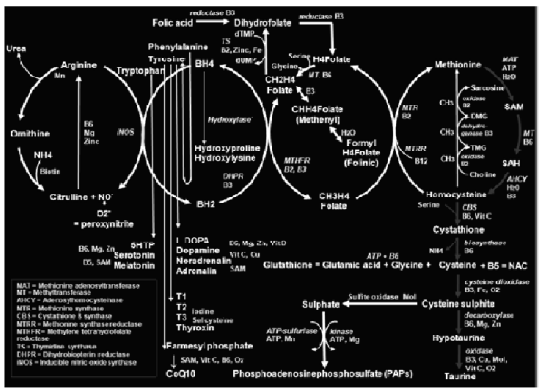
APO E4 is thought not to be a determinate in Alzheimer's but maybe a risk factor.

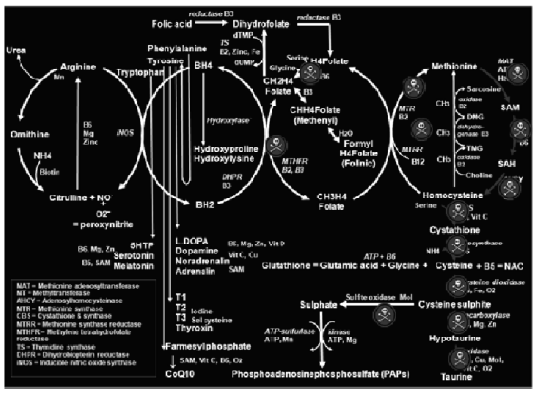
Epigenetic intervention can give powerful intervention to help especially with SNIP's.

Methylation

Some Neurological Methylation Functions
Synthesis of some phospholipids
DNA methyltransferase
Methyl Caps DNA /RNA
Synthesis of myelin




Folic acid
Dihydrofolate
dTMP
Urea
Arginine
Phenylalanine
Tyrosine
Tryptophan
BH4
Ornithine
NH4
Biotin
Citrulline + NO
O2-
= peroxynitrite
Hydroxyproline
Hydroxylysine
BH2
CH2H4 Folate
CHH4Folate (Methenyl)
H2O
Formyl H4Folate (Folinic)
CH3H4 Folate
Methionine
SAM
SAH
Choline
Homocysteine
Serine
Cystathione
Glutathione = Glutamic acid + Glycine + Cysteine + B6 = NAC
L DOPA
Dopamine
Noradrenalin
Adrenalin
5HTP
Serotonin
Melatonin
T1
T2
T3
Thyroxin
Farnesylphosphate
CoQ10
Sulphate
Cysteine sulphite
Hypotaurine
Taurine
Phosphoadenosinephosphosulfate (PAPs)


Folic acid
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Tyrosine
Tryptophan
BH4
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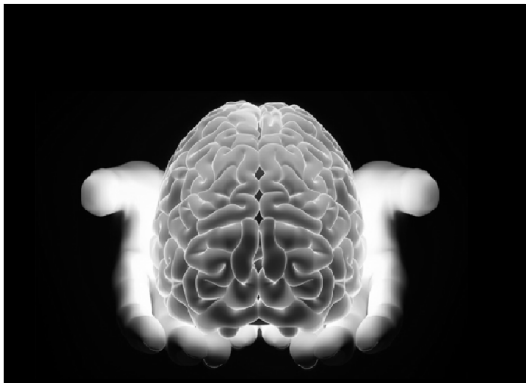
Citrulline + NO
O2-
= peroxynitrite
Hydroxyproline
Hydroxylysine
BH2
CH2H4 Folate
CHH4Folate (Methenyl)
H2O
Formyl H4Folate (Folinic)
CH3H4 Folate
Methionine
SAM
SAH
Choline
Homocysteine
Cystathione
Glutathione = Glutamic acid + Glycine + Cysteine + B6 = NAC
L DOPA
Dopamine
Noradrenalin
Adrenalin
5HTP
Serotonin
Melatonin
T1
T2
T3
Thyroxin
Farnesylphosphate
CoQ10
Sulphate
Cysteine sulphite
Hypotaurine
Taurine
Phosphoadenosinephosphosulfate (PAPs)

HYPOXIA



Hypoxia is a condition in which the body or a region of the body is deprived of adequate oxygen supply.

Hypoxia may be classified as either *generalized*, affecting the whole body, or *local*, affecting a region of the body.

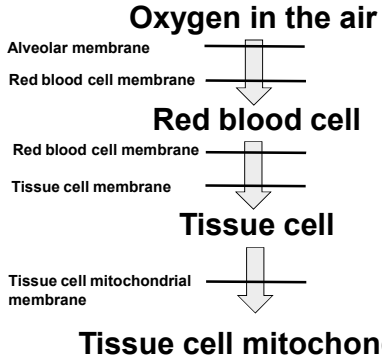
Symptoms
Gradual onset - Light-headedness
Numbness / tingling of extremities,
Nausea and anorexia.
Tiredness
Visual deterioration
Memory loss
Feeling the cold
Degenerative changes

Hypoxia can result from a failure at any stage in the delivery of oxygen to cells. This can include decreased partial pressures of oxygen, problems with diffusion of oxygen in the lungs, insufficient available haemoglobin, problems with blood flow to the end tissue, and problems with breathing rhythm.

Patient Protocol for Hypoxia

From weakness patient strengthens to HYPOXIC eye position
Confirm using OXYGEN vial to strengthen
Challenge using following vials

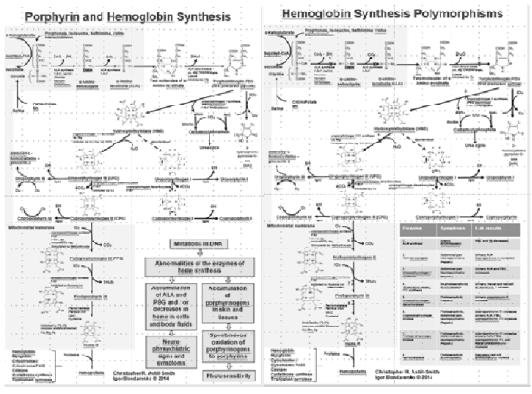
PHOSPHOLIPIDS	HEMOGLOBIN	Co-ENZYME Q10
EPO, BSO , Borage	ALA	Co-Q10 in oil
Black cumin	PBG	
Flax , Chia	UPG III	
Grape seed	CPG III	
Hazelnut, Hemp	PP IX	
Macademia		
Olive, Coconut		
Peanut		
Pumpkin		
Super Omega 3		
Walnut		
WGO		

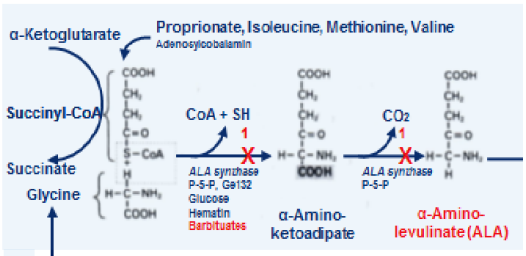


Hemoglobin and Myoglobin contain heme, a cyclic tetrapyrrole consisting of 4 molecules of pyrrole. One atom of ferrous iron resides at the centre.

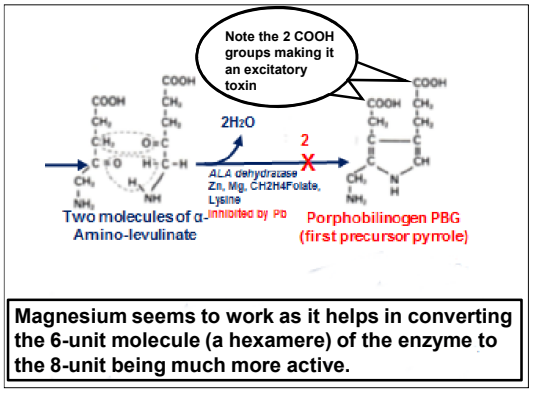
Heme-dependent enzymes

Catalase
Myeloperoxidase
Eosinophil peroxidase
Various peroxidases
i-Nitric Oxide Synthase (iNOS)
Cystathione synthase
Cytochrome p450
Cytochromes for energy production
Sulfite oxidase
Thyro-peroxidase
COX 1 and COX 2 **Tryptophane pyrrolase**

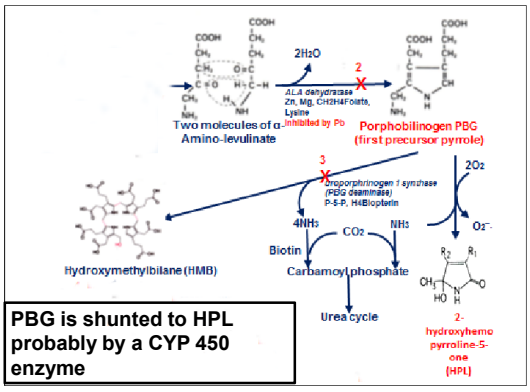




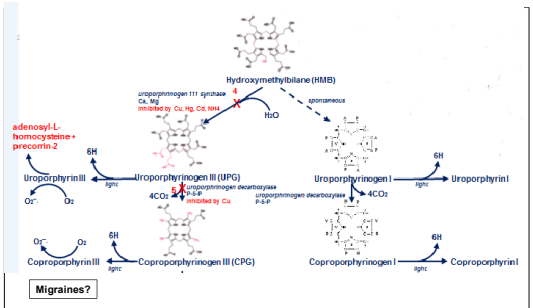
Succinyl CoA is formed in the Krebs' cycle



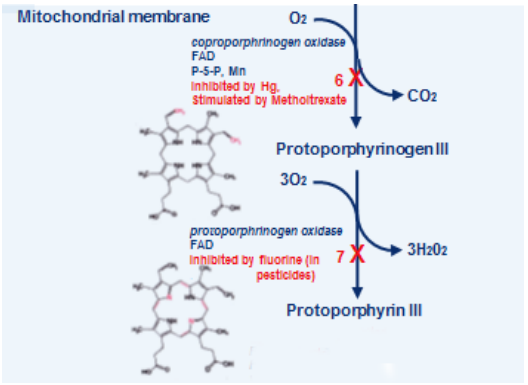
Magnesium seems to work as it helps in converting the 6-unit molecule (a hexamere) of the enzyme to the 8-unit being much more active.

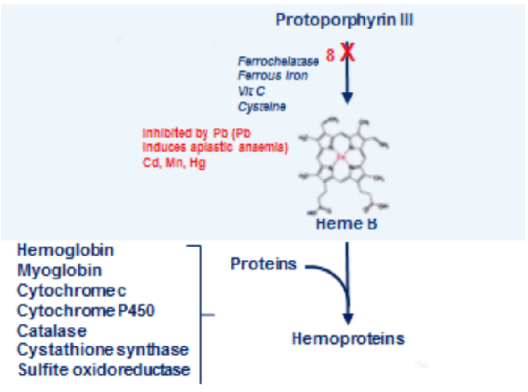


PBG is shunted to HPL probably by a CYP 450 enzyme



Always challenge with mauve acetate when high Urophorphyrin III or Coproporphyrin III





Alzheimer's disease is being linked to porphyria also. In 2004 some 4.5 million Americans were said to have the disease.
By age 85 one out of two Americans has Alzheimer's!

Myelin damage resulting from B_{12} deficiency, even in the presence of adequate folate and methionine, is more specifically and clearly a vitamin deficiency problem. It has been connected to B_{12} most directly by reactions related to *MUT*, which is required to convert methylmalonyl coenzyme A into succinyl CoA.

Failure of this second reaction to occur results in elevated levels of MMA, a myelin destabilizer. Excessive MMA will prevent normal fatty acid synthesis, or it will be incorporated into fatty acid itself rather than normal malonic acid.

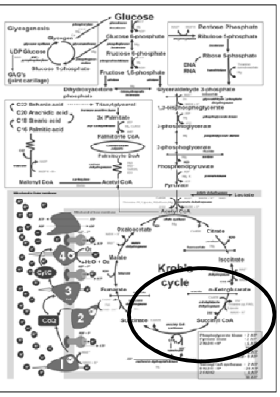
If this abnormal fatty acid subsequently is incorporated into myelin, the resulting myelin will be too fragile, and demyelination will occur.

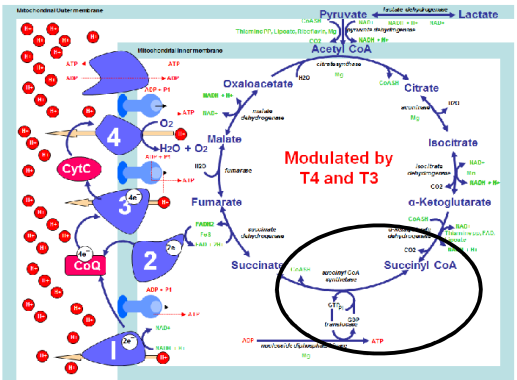
Methylmalonyl CoA is formed as an intermediate in the catabolism of valine and by the carboxylation of proprionyl CoA arising in the catabolism of isoleucine, cholesterol and odd numbered fatty acids or directly from proprionate a major product of microbial fermentation especially when clostridium is present.

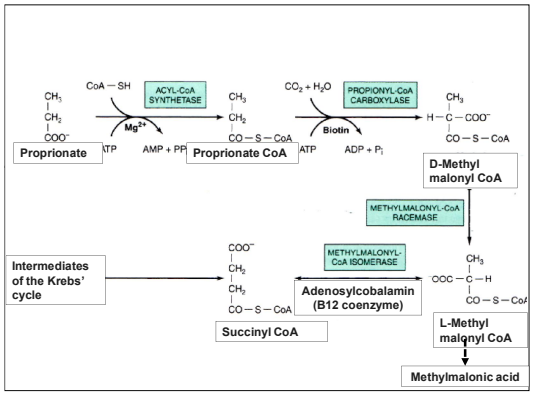
Proprionic acid in stool analysis showed much higher levels in Europeans than in African in Africa.
High proprionic acid adversely influences brain function.

Energy production

1. Glycolysis
2. Krebs' Cycle
3. Electron transport







Probiotics

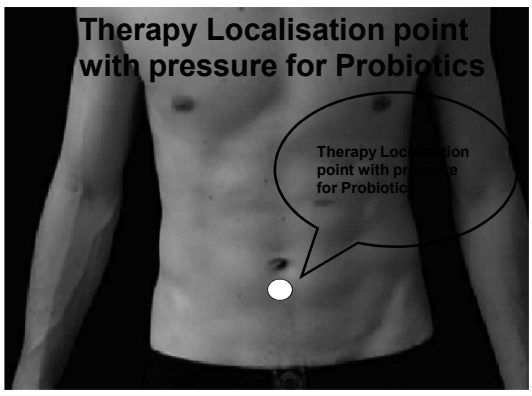
Microbiome disturbance is due to the food we eat.
Gut organisms contain 99% of the genetic material in our bodies. It is a DNA store. It influences the brain.
Antibiotics and over hygiene effects the biome and increases the risk of Alzheimer's.

People with the greatest diversity of the biome have the lowest incidence of Alzheimer's.
Diversity increases gut integrity.
Gram negative bacteria (Clostridium – C.difficile) increase Lipopolysaccharide (LPS) which creates inflammation and permeability especially in autism, Parkinson's and Alzheimers.

Proprionic acid (C3) is a metabolic poison. It increases Omega 6 to Omega 3 ratios, alters neurotransmitters, influences glutamate influx into the mitochondria.

Bifidobacteria Bifidus
Lactobacillus Acidophilus
Lactobacillus Bulgaricus
Lactobacillus Casei
Lactobacillus Plantarium
Lactobacillus Rhamnosus
Streptococcus thermophilus

Smart Probiotic



Terminal Lucidity
Many people have experienced the astonishing clarity of mind that often comes to demented elderly people just before they pass on. This is known as "terminal lucidity".
There is no scientific explanation for this.

Stages in Healing the Brain

Glial cells make up 85% of all the cells in the brain. Their main function is detoxification.

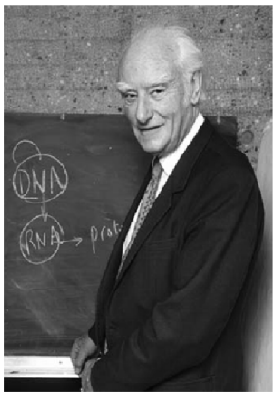
The blood brain barrier is there to protect the brain from toxins..

The brain has no lymphatic system.

1. Neuronal Stimulation.
Light
Sound
Electricity
Vibration
Movement
Thought
all help to revive dormant neurones.

Optagenetics
The "far-fetched" possibility of using light for selectively controlling precise neural activity (action potential) patterns within subtypes of cells in the brain was articulated by Francis Crick in his Kuffler Lectures at the University of California in San Diego in 1999.

Francis Crick was the first person to propose that light may switch on some neurones and switch off others.



2. Improve state to regulate and modulate the brain to achieve homeostasis.
Thoughts turn on some neurones and others off. Once neurones are turned on by thought then blood flows in the area.
Internal neurostimulation using thought helps the brain to build new circuits.

3. Neuromodulation is the balance between excitation and inhibition and quietens the noisy brain.
Works on the Reticular Activating System (RAS) in the brain stem.
Stimulation by light, sound, vibration, electricity all resets the RAS.

Autonomic Nervous System resetting is by neuromodulation.
Increased sympathetic system leads to poor healing.
Increased parasympathetic leads to rest, digest and repair.
Increases sleep, growth and repair, recharges the mitochondria, turns on social engagement systems.

4. Neural Relaxation
Sleep catch up. In sleep the glial cells open up and detox. They are 10x more active then than in the awaken state.
Too little sleep leads to a toxic brain.
Too much sleep increases the risk to stroke????

5. Neural Differentiation and Learning
Brain does best in making fine decisions or differentiations. Exercises that make subtle distinctions like in light and sounds are best.

Examining a Patient

"We are a composite of multiple systems. Pay attention to the web of interrelating factors"

Jeffrey Bland PhD

Markers for examing people with Memory Loss
Amyloid beta protein fragment 1-42

ENERGY
Mg-ATP
DNA Polymerase
CoQ10 (Ubiquinone)
Complex III Cytochrome c reductase
Cytochrome C
Complex IV Cytochrome c oxidase
Cardiolipin
CO
CN
Malondialdehyde

HYPOXIA
O2
Hemoglobin
ALA
PBG
Uroporphyrin III
Coproporphyrin III
Protoporphyrin IX
Heme

Homocysteine
APOE4
Probiotics

1. Check for strong indicator muscle. Tap cross extensor reflexes for major mechanical faults.
2. Challenge for body type colour
3. Challenge for any sub-conscious emotional imbalance
4. Challenge for cranial fault(s)

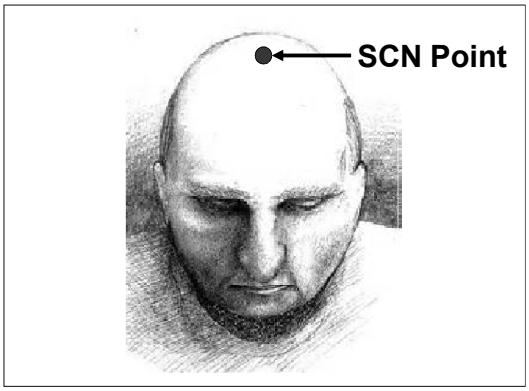
The primary circadian "clock" in mammals is located in the suprachiasmatic nuclei (SCN), a pair of distinct groups of cells located in the hypothalamus. The retina of the eye contains "classical" photoreceptors ("rods " and "cones"), which are used for conventional vision.

The retina also contains specialized ganglion cells that are directly photosensitive, and project directly to the SCN, where they help in the entrainment of this master circadian clock. These cells contain the photo-pigment melanopsin and their signals follow a pathway called the retinohypothalamic tract leading to the SCN.

The SCN is responsible for controlling circadian rhythms. The neuronal and hormonal activities it generates regulate many different body functions in a 24-hour cycle, using around 20,000 neurons. The SCN interacts with many other regions of the brain.

Many aspects of mammalian behaviour and physiology show circadian rhythmicity, including sleep, physical activity, alertness, hormone levels, body temperature, immune function, and digestive activity.

The SCN also controls "slave oscillators" in the peripheral tissues, which exhibit their own ~24-hour rhythms, but are kept in synchrony by the SCN.



Cranial Faults

Any weakness is negated by Deep Inspiration or Deep Expiration or both when there is a Compression.

<u>Treatment using TLT</u>

1. **Practitioner does spiral field stimulation before treatment.**
2. **Practitioner TL's both patient's eyes.**
3. **Practitioner TL's own eyes.**
4. **Practitioner occludes own jaw for 1 minute at 1hz**

<u>Sutural Technique</u>

There will be 3 sagittal plane suture jammings

1. **Intermaxillary suture**
2. **Sagittal suture**
3. **Pubic symphysis**

Intermaxillary suture

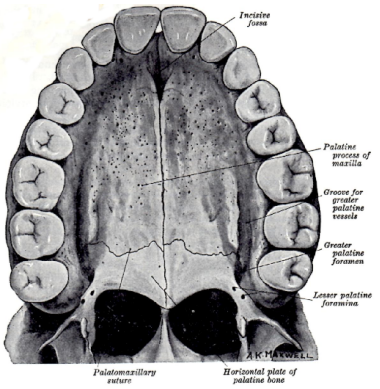
From the ICAK presentations of Agne and Rosalie Cervo Peres.

Cervicals

Thoracics

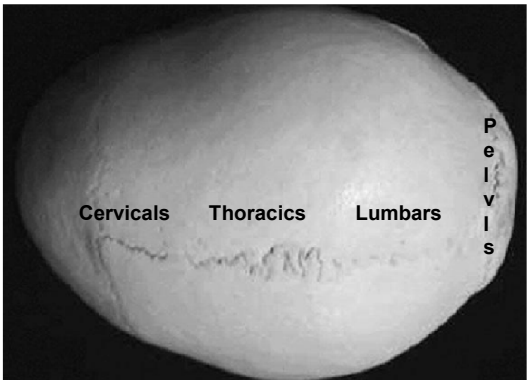
Lumbars

Pelvis



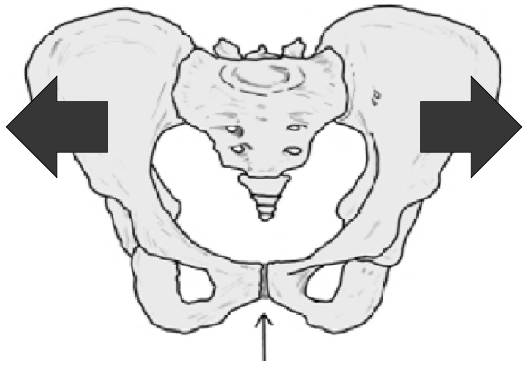
1. **Identify suture jamming by Therapy Localisation**
2. **Challenge for phase of respiration that negates TL – usually inspiration**
3. **Patient places their thumbs on gum adjacent to positive TL**
4. **Patient pulls outwards gently 6x on inspiration**

Sagittal suture



1. **Identify suture jamming by Therapy Localisation**
2. **Challenge for phase of respiration that negates TL – usually inspiration**
3. **Doctor places his fingers adjacent to positive TL**
4. **Doctor spreads suture outwards gently 6x on inspiration**

Pubic symphysis

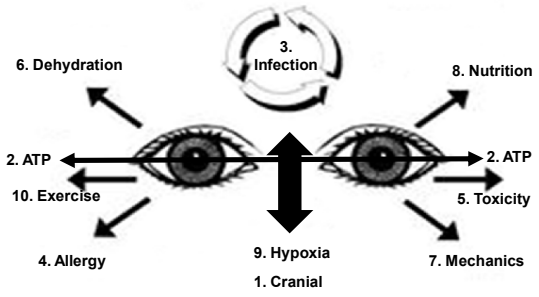


1. **Identify symphysis jamming by Therapy Localisation**
2. **Challenge for phase of respiration that negates TL – usually inspiration**
3. **Doctor places his hands medial to the ASIS's**
4. **Doctor spreads symphysis outwards gently 6x on inspiration**

Eyes into Distortion (EID)

1. In the clear from strength to challenge for any weakening eye positions.
2. From any positive TL thus from weakening to challenge for any strengthening eye positions.
3. From primary meridian alarm point thus from weakening to challenge for any strengthening eye positions.

Eyes into Distortion (EID)



Hierarchy of Disease

Emotion
Hypoxia
Nutritional deficiency
Mechanical dysfunction
Dehydration
Toxicity
Allergy
Infection
ATP

ATP

Weakening will be negated with challenging with Mg-ATP.

1. **Challenge against DNA polymerase. If strengthens prescribe Zinc for DNA repair.**
2. **Re-challenge eye position. If weakness returns challenge with nutritional composites e.g. Minerals, Vitamins, Fat soluble vitamins, Co-enzymes, Fatty acids, Probiotics.**

Infections
Challenge against
BACTERIA
ACUTE and POST VIRUS
FUNGUS
PARASITES
- **PROTOZOA**
- **SPORAZOA**
- **NEMATODE**
- **TREMATODE**
- **CESTODE**

Bacteria –
- **Inositol**
- **Zinc**
- **Arginine**
- **Olive leaf**

- **Ginger**
- **Ionic silver**
- **Mannose**
- **Thiamine / Silver**
- **Golden seal**

Virus –
- **Iron**
- **Zinc**
- **Vitamin C**
- **Echinacea**
- **Ionic silver**
- **Astragalus**
- **Selenium**
- **Garlic**
- **Golden seal**
- **Olive leaf**

Parasites – **Iodides**
Garlic
Cumin / Cloves
Black walnut tincture
AP formula
Ginger / Turmeric
RED, GREEN, BLUE
Spice mixes
Coriander for cestodes
Cloves or nutmeg for nematodes

Fungi – **Zinc**
Oregano
Probiotics
Sodium sulfate
Coconut oil
Coriander
Ginger
Other spices
Pau d'arco
AF Cream locally

Allergy

Allergen something
Eaten
Drunk
Inhaled
Transdermal

Identify and remove from exposure.
Look specially for Gluten intolerance
Use Yarrow to supersede challenge.

Toxins

Challenge against

CHEMICALS
TOXIC METALS esp Hg and Al
RADIATION

Toxins

Chemicals -
- Black walnut
- Coriander spice
- NAC
- Lemon balm
- Rosemary
- Yarrow
- Other spices
- Charcoal

Toxins

Toxic metals –
- Black walnut
- Coriander herb
- Coriander spice
- Lemon balm
- α-Lipoic acid
- Yarrow
- Glutathione

Vitamin C for nickel

Magnesium for Aluminium

Toxins

Radiation -
- Chlorella
- Coriander spice
- Smart Vitamin C (Rutin)
- Turmeric
- Yarrow

Dehydration

1-2 litres per day
Ideally in glass bottles or titrate into Miron Glass 1 litre bottles
Calcium / Magnesium ratio 2:1 or less
Sodium < 20ppm
pH 7.4

Structure

1. Cervical spine
2. Thoracic spine
3. Diaphragm (TL Kid 22)
4. M/S joint
5. Sternoclavicular joint
6. Acromioclavicular joint
7. Ribs
8. Lumbar spine
9. Upper extremity
10. Lower extremity

Nutrition

Challenge with nutritional composites e.g. Minerals, Vitamins, Fat soluble vitamins, Co-enzymes, Fatty acids, Probiotics, Saccharides.

Re-challenge eye position. If weakness returns challenge with nutritional composites again and repeat until clear.

Hypoxia

Weakness negated with O2
Maybe due to
1. **Phospholipid deficiency**
2. **Hemoglobin**
3. **Co-Q10**

Patient Protocol for Hypoxia

From weakness patient strengthens to HYPOXIC eye position
Confirm using OXYGEN vial to strengthen
Challenge using following vials

PHOSPHOLIPIDS	HEMOGLOBIN	Co-ENZYME Q10
EPO, BSO , Borage	Adenosylcobalamin	Co-Q10
Black cumin	Zinc	
Flax , DHA	Magnesium	
Grape seed	CH2H4Folate	
Hazelnut, Hemp	H4Biopterin	
Macademia	Biotin	
Olive, Coconut	P-5-P	
Peanut	Manganese	
Pumpkin	Vitamin C	
Super Omega 3	Lutein	
Walnut		
WGO		

Dr David Perlmutter'sTop Seven Brain Boosting Supplements

1. **Smart DHA**
2. **Smart Vitamin E**
3. **Smart Turmeric**
4. **Smart Probiotics**
5. **Coconut oil**
6. **α-Lipoic Acid**
7. **Smart Vitamin D3**

Bruce Ames Formula
Acetyl-L Carnitine 400mg
+
α-Lipoic acid 100mg

Other Supplements to consider
CoQ10
Hydroxycobalamin
- **Adenosylcobalamin**
- **Methylcobalamin**

Folates
Smart Magnesium
Choline
Smart Zinc
Thiamine

Other Supplements to consider
Reduced Glutathione
Smart Lutein
Biotin
Ginkgo biloba
Lemon balm
Rosemary
Black walnut
Cinnamon
Green Tea