

The Ability of Nutrients to Promote Brain Plasticity and Cognitive Health

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The Economist - Natasha Loder, Barry Downard

Table 1 | **Select nutrients that affect cognitive function**

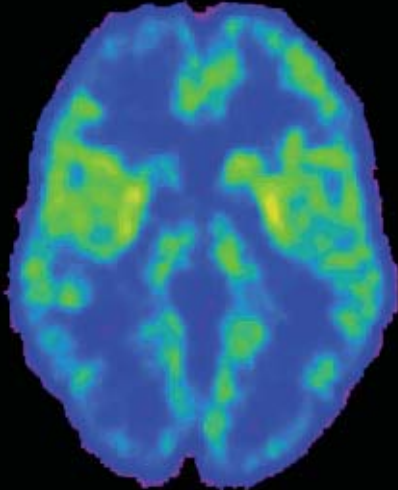
Nutrient	Effects on cognition and emotion	Food sources
Omega-3 fatty acids (for example, DHA)	Amelioration of cognitive decline in the elderly ¹⁴⁸ ; basis for treatment in patients with mood disorders ⁹⁰ ; improvement of cognition in traumatic brain injury in rodents ⁹¹ ; amelioration of cognitive decay in mouse model of Alzheimer's disease ^{149,150}	Fish (salmon), flax seeds, krill, chia, kiwifruit, butternuts, walnuts
Curcumin	Amelioration of cognitive decay in mouse model of Alzheimer's disease ¹²³ ; amelioration of cognitive decay in traumatic brain injury in rodents ⁸⁹	Turmeric (curry spice)
Flavonoids	Cognitive enhancement in combination with exercise in rodents ⁹² ; improvement of cognitive function in the elderly ¹⁵¹	Cocoa, green tea, Ginkgo tree, citrus, wine (higher in red wine), dark chocolate
Saturated fat	Promotion of cognitive decline in adult rodents ⁴ ; aggravation of cognitive impairment after brain trauma in rodents ⁸⁸ ; exacerbation of cognitive decline in aging humans ³	Butter, ghee, suet, lard, coconut oil, cottonseed oil, palm kernel oil, dairy products (cream, cheese), meat
B-vitamins	Supplementation with B6, B12 or folate has positive effects on memory performance in women of various ages ¹⁵² ; vitamin B12 improves cognitive impairment in rats fed a choline-deficient diet ¹⁵³	Various natural sources, B-12 not available from plant products
Vitamin D	Important for preserving cognition in the elderly ¹⁵⁴	Fish liver, fatty fish, mushrooms, fortified products, milk, soy milk, cereal grains
Vitamin E	Amelioration of cognitive impairment after brain trauma in rodents ¹⁰² ; reduces cognitive decay in the elderly ¹¹⁹	Asparagus, avocado, nuts, peanuts, olives, red palm oil, seeds, spinach, vegetable oils, wheat germ
Choline	Reduction of seizure-induced memory impairment in rodents ¹⁵⁵ ; a review of the literature reveals evidence for a causal relationship between dietary choline and cognition in humans and rats ¹⁵⁶	Egg yolks, soy beef, chicken, veal, turkey liver, lettuce
Combination of vitamins (C, E, carotene)	Antioxidant vitamin intake delays cognitive decline in the elderly ¹⁵⁷	C: citrus fruits, several plants and vegetables, calf and beef liver. E: see above
Calcium, zinc, selenium	High serum calcium is associated with faster cognitive decline in the elderly ¹⁵⁸ ; reduction of zinc in diet helps to reduce cognitive decay in the elderly ¹⁵⁹ ; lifelong low selenium level associated with lower cognitive function in humans ¹⁶⁰	Calcium: milk, coral. Zinc: oysters, a small amount in beans, nuts, almonds, whole grains, sunflower seeds. Selenium: nuts, cereals, meat, fish, eggs
Copper	Cognitive decline in patients with Alzheimer's disease correlates with low plasma concentrations of copper ¹⁶¹	Oysters, beef/lamb liver, Brazil nuts, blackstrap molasses, cocoa, black pepper
Iron	Iron treatment normalizes cognitive function in young women ¹⁶²	Red meat, fish, poultry, lentils, beans

Nutrients examined in animal models of TBI

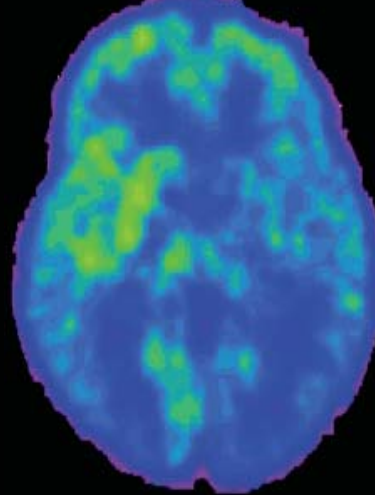
- Omega-3 fatty acids
- Curcumin (turmeric)
- Antioxidants: flavonoids, Vitamin E
- Ketogenic diet
- Dietary restriction or fasting
- Dietary branched chain amino acids
- Caffeine

The pathobiology of TBI

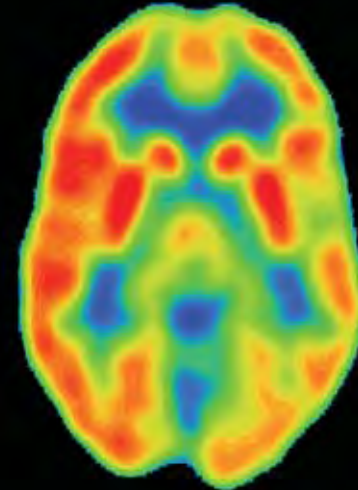
Mild GCS 15



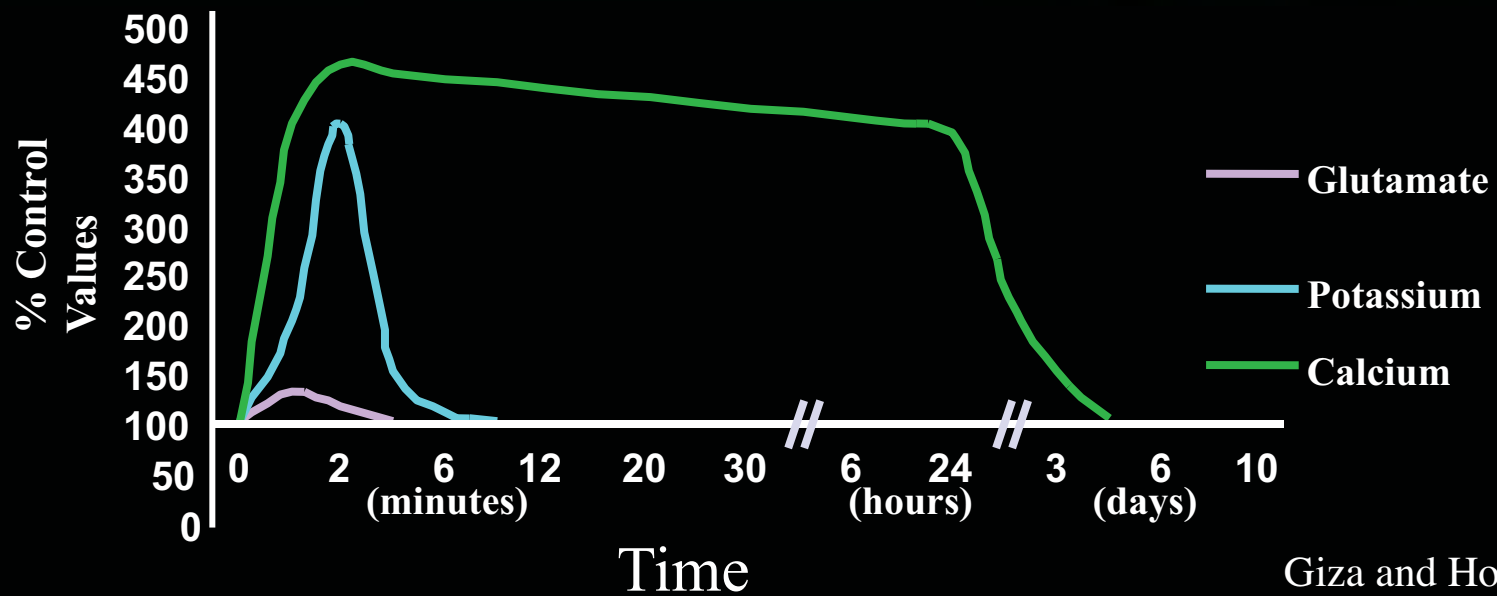
Severe GCS 5



Normal



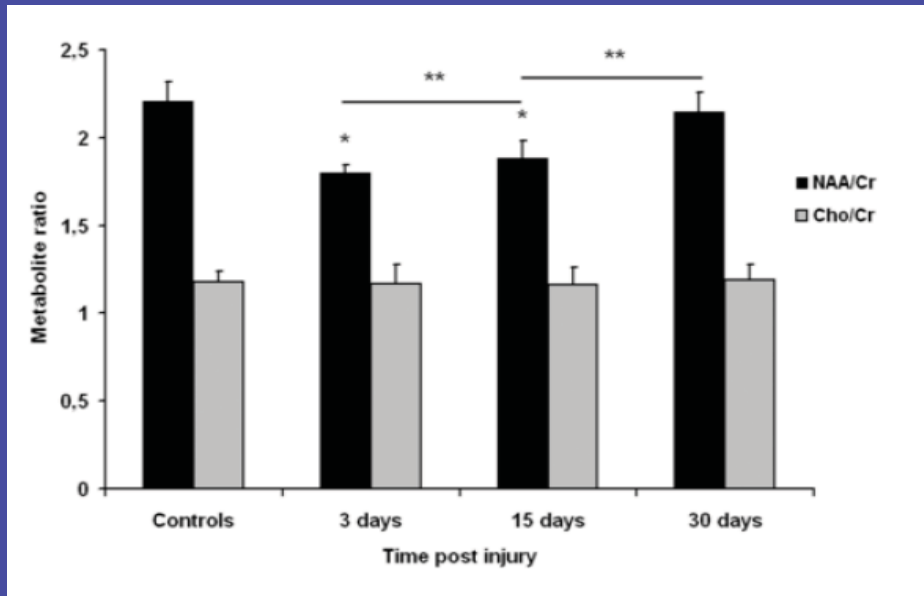
Metabolic dysfunctional (depression) cascade following TBI



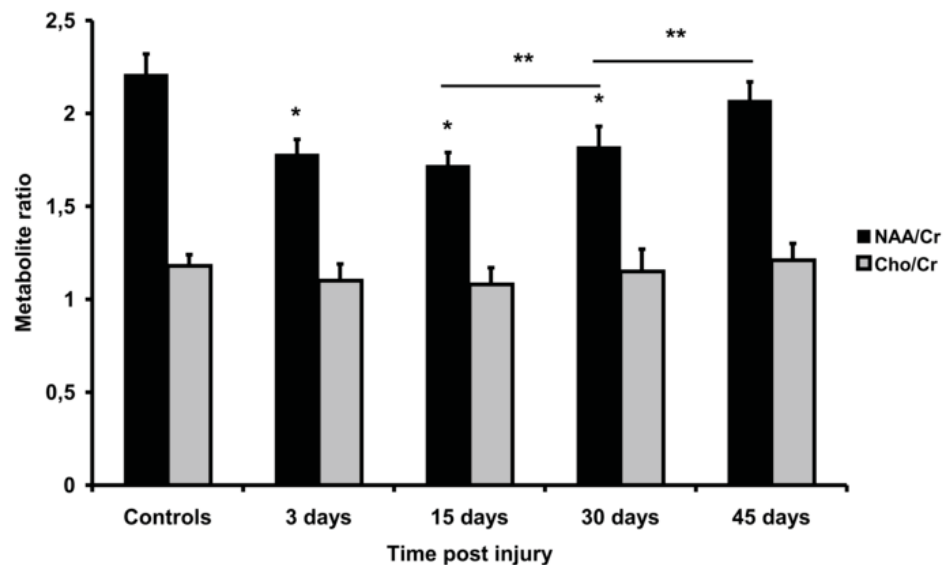
Giza and Hovda, 2001

The period of brain vulnerability following TBI is extended following a second concussion

N-acetylaspartate (NAA) was assessed using spectroscopy in athletes (n=10) suffering single concussion Vs age-matched controls (n=5)



Athletes Sustaining 2 Concussions Between the 10th and 13th Day after the First Concussion

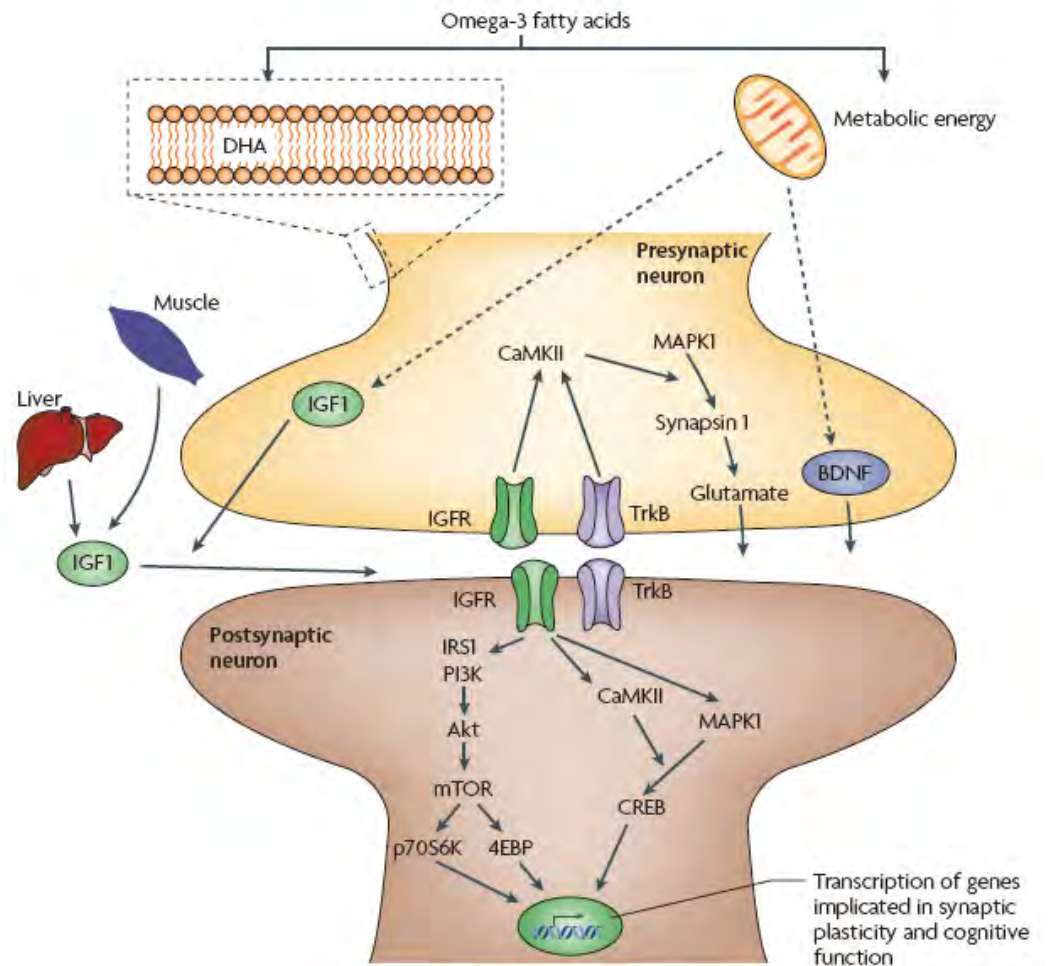


Vagnozzi et al. 2008

Desirable objectives to moderate cognitive and emotional distress after TBI:

- To reduce energy crisis and promote membrane repair
- To elevate the potential for synaptic plasticity
- To support neuronal signaling
- To stimulate mechanisms that can provide broad protection

Can nutrients help accomplishing these goals?



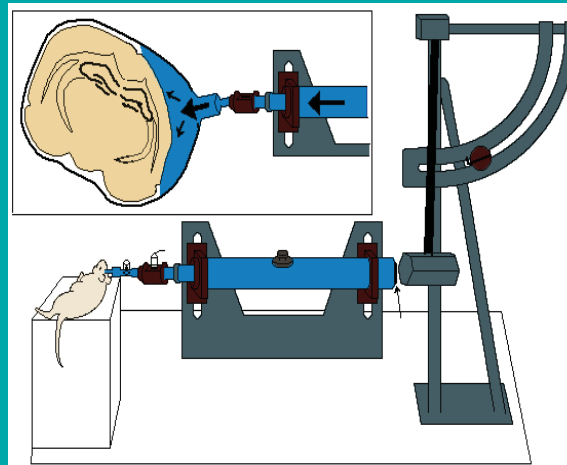
Gomez-Pinilla, Nature Rev. Neurosci, July 2008

Ketogenic diet

- Used successfully to treat a variety of epilepsy syndromes
- More recently evaluated in TBI as a way to elevate alternative fuels during brain metabolic depression (β -hydroxybutyrate, Prins, 2008)
- Effective in animal models of TBI during the period of brain development (Prins, 2005).
- Maybe involved with the neuroprotective effects of fasting (Davis et al, 2008)
- Samoilova et al (Samoilova et al., 2010) showed that in vitro treatment with the ketone body D- β -hydroxybutyrate protected culture against chronic hypoglycemia, oxygen-glucose deprivation, and excitotoxicity, independent of seizure control. Effects of ketosis seem related to control of metabolic stress
- Ongoing research to test the effects of other alternative fuels (i.e., lactate, piruvate) during the period of metabolic depression after TBI

Animal model of concussive injury...

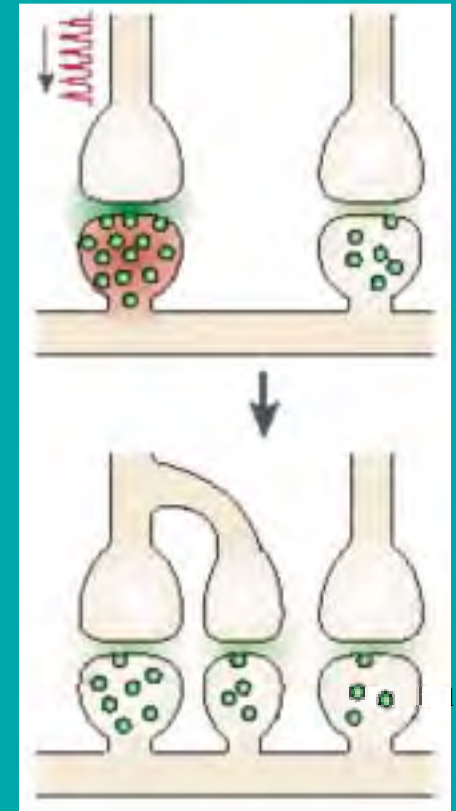
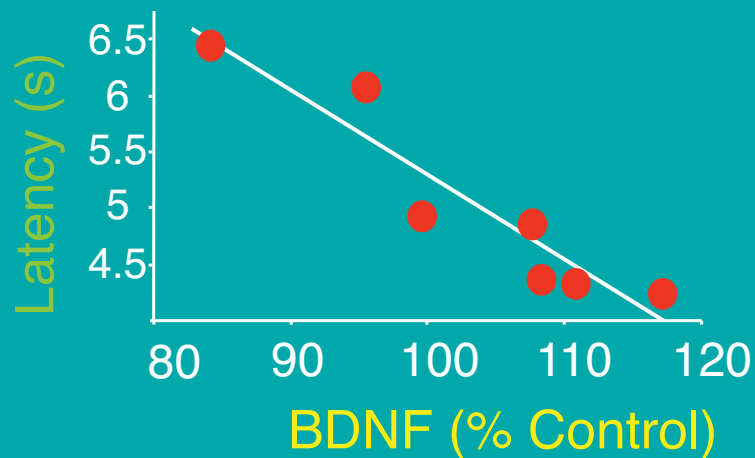
- Concussive injury results in cognitive and emotional abnormalities in spite of minimal neuronal death
- Fluid percussion injury (FPI) can reproduce several of the features of human concussion



Brain-derived neurotrophic factor (BDNF) important for learning and memory, and mood

- strong promoter of neuronal excitability
- released in response to synaptic activity
- strong synaptic facilitator (behavior is controlled at the synapse)
- Abundant in hippocampus

Low levels of BDNF have associated with poor learning performance is associated and depression

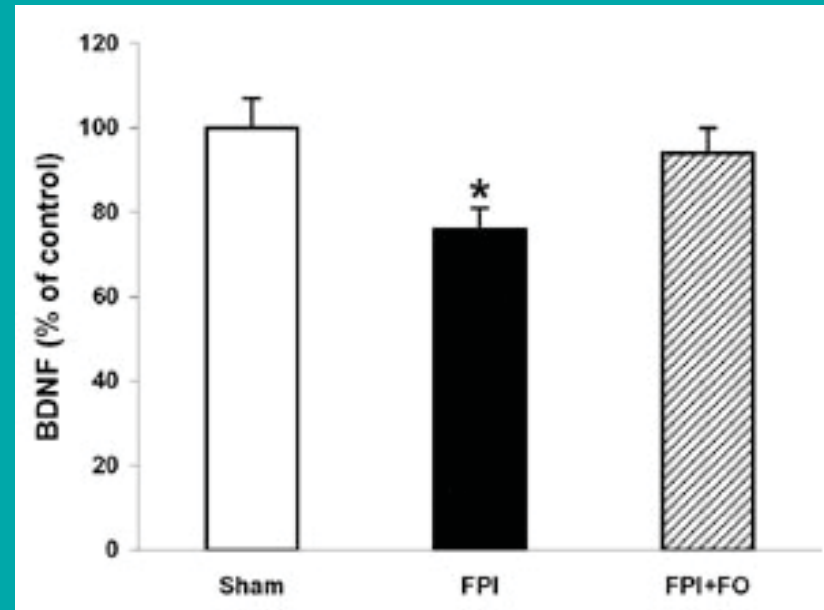
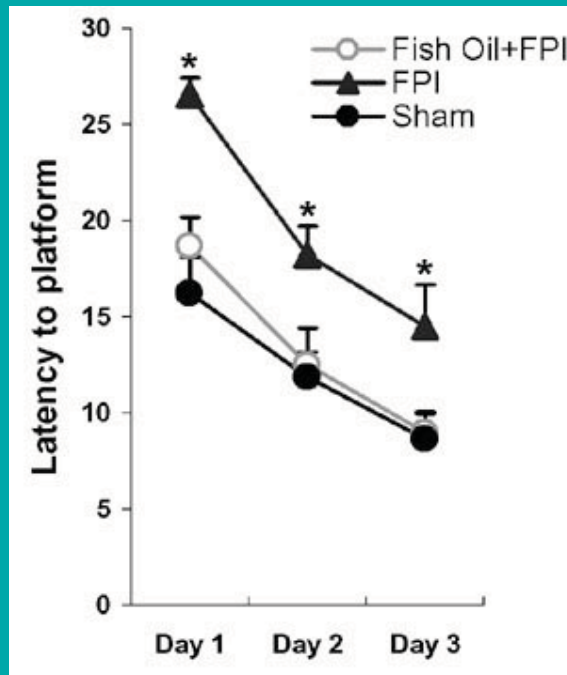


Omega-3 fatty acid DHA is brain food

- DHA is very high in brain (~31% of FA in PE in cortex) -- major component of gray matter nerve membranes, particularly at synaptic terminals
- Essential fatty acids- The body cannot synthesize Omega-3 fatty acids
 - **Linolenic acid (18:3 n-3) >>>docosahexanoic acid (DHA, n-3)**
- Anti-inflammatory and antioxidant capacities
- DHA (fish, algae) is crucial in brain/retina development and CNS maintenance in adults
- susceptible to oxidative attack because six double bonds
- DHA insufficiency affect membrane fluidity, serotonin transport, gene transcription, inflammation, and energy metabolism in the brain



Protective effects of Fish oil dietary supplementation in TBI



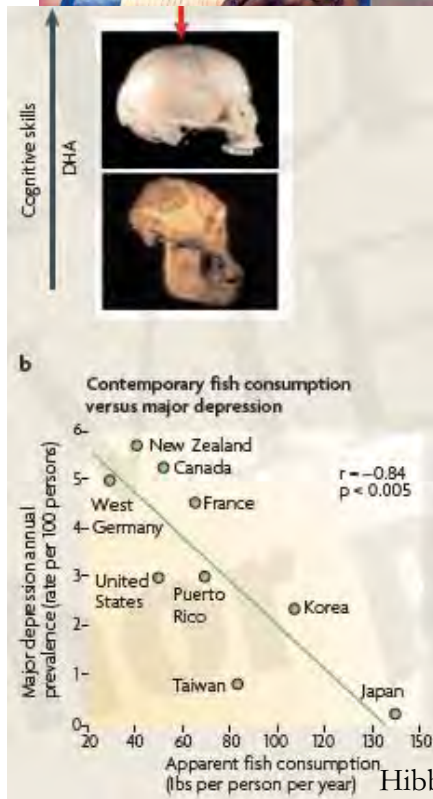
- Regular diet: 0.04% DHA; EPA: 0.045%
- Fish Oil diet: 1.28% DHA; EPA: 1.39%

FO diet started 3 weeks before FPI

(Similar effects when started immediately after FPI)



DHA is crucial building material for brain under development
How do levels of dietary DHA during brain development affect adult plasticity?



The making of a large brain requires a high quality diet and efficient use of energy. Cognitive skills evolved along the making of a larger brain

Hibbeln JR. *Lancet* 1998

Gomez-Pinilla, *Nature Rev. Neurosci*, July 2008

Curcumin (turmeric)



Turmeric plant

Anti-inflammatory, Anti-oxidant, Anti-mutagenic

Curcumin is one of the most prevalent nutritional and medicinal compounds in India; main candidate responsible for reduced (4.4-fold) prevalence of Alzheimer's disease (AD) in India compared to USA (Ganguli et al., 2000 Arch Neurol 57:824)

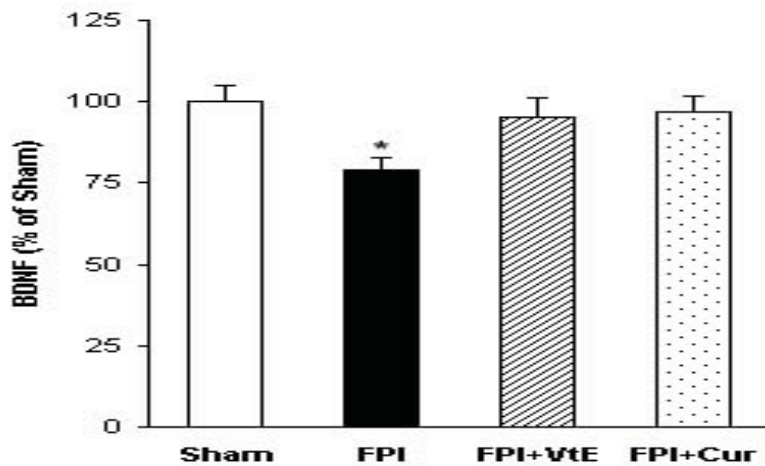
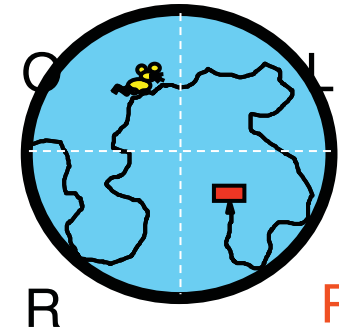
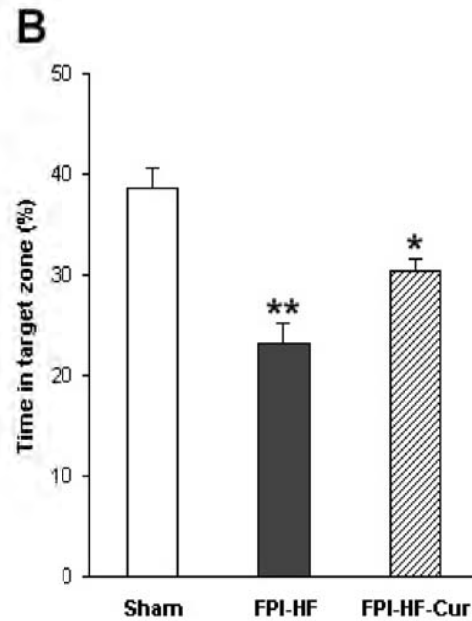
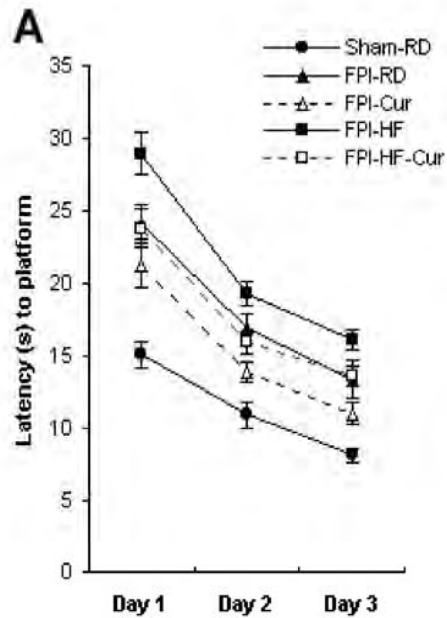
Several studies have confirmed its neuroprotective role in various neurodegenerative conditions such as

Alzheimer's Disease (Lim et al., 2001 The Journal of Neuroscience, 21(21):8370-8377),

Cerebral ischemia (Zhao et al., 2008 Brain Research 1229:224-232) and also in

Traumatic Brain Injury (Wu et al., 2006 Experimental Neurology 197:309-317).

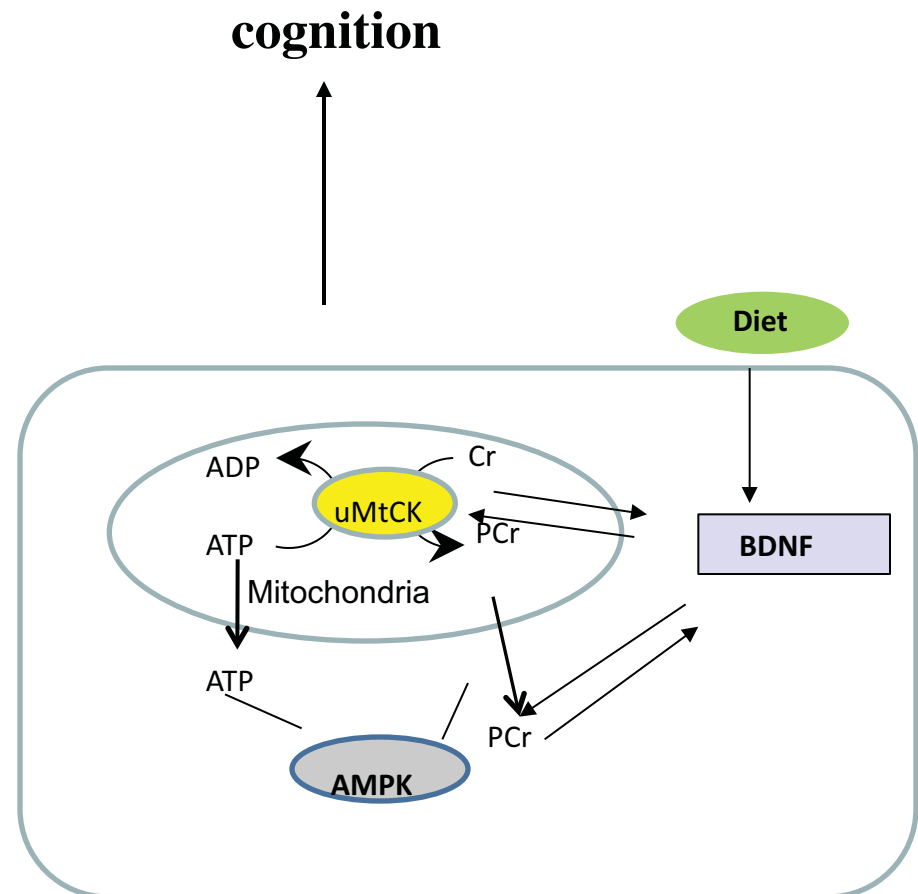
Curcumin reduces the cognitive impairment associated with brain trauma



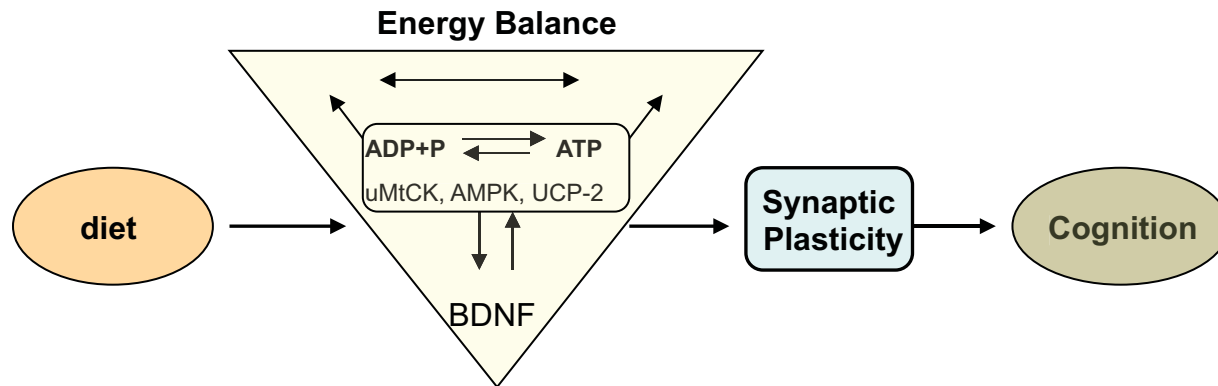
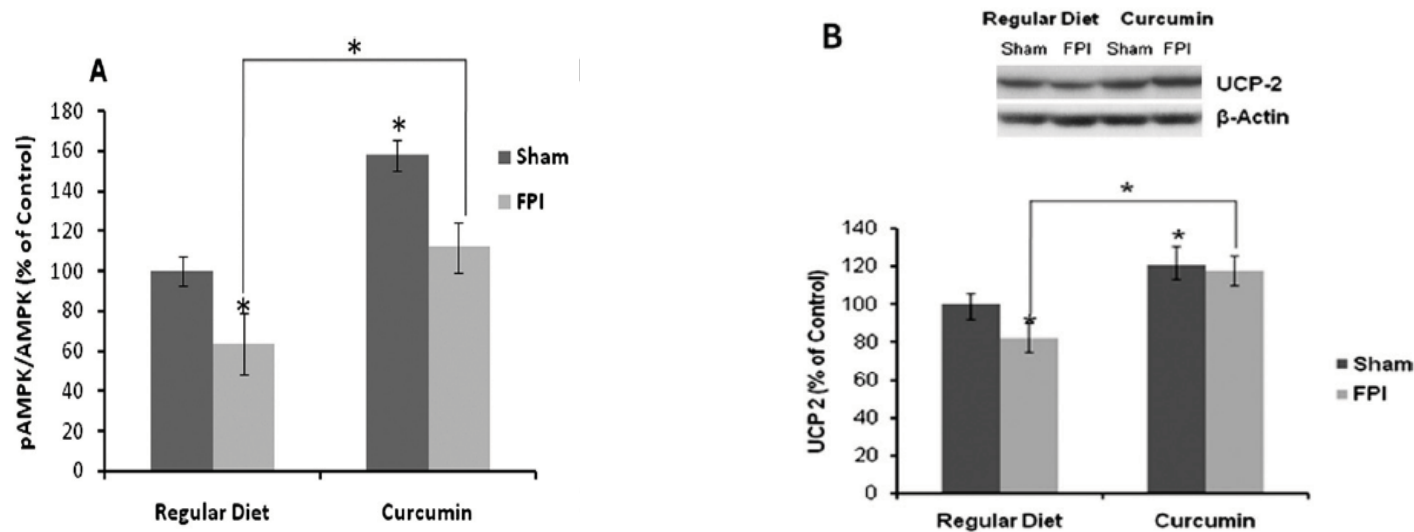
Curcumin applied 3 weeks before FPI

Mechanisms procuring efficient use of energy interface with molecular systems important for cognition

- **BDNF** increases mitochondrial activity (El Idrissi & Trenker, 1999), and glucose utilization (Birkhalter et al., 2003). BDNF regulates glucose and insulin levels and body weight - Mice with reduced BDNF levels are obese (Kernie et al., 2000)
- **uMtCK** is involved in energy transduction, and modulates cognitive function (Boero, 2003)
- **AMPK** is a kinase that increases cell energy supply by turning on catabolic pathways that generate ATP while switching off pathways that consume ATP (Hardie, 1998,1999). Support learning
- **UCP2** is found in hippocampal synaptic membranes (Horvarth, 2003, Rowland, 2000) and modulates ATP production, and oxidative stress by uncoupling proton gradient from ATP synthesis

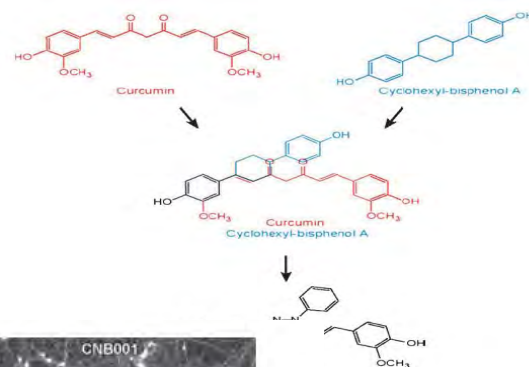


Curcumin helps stabilize energy homeostasis after TBI

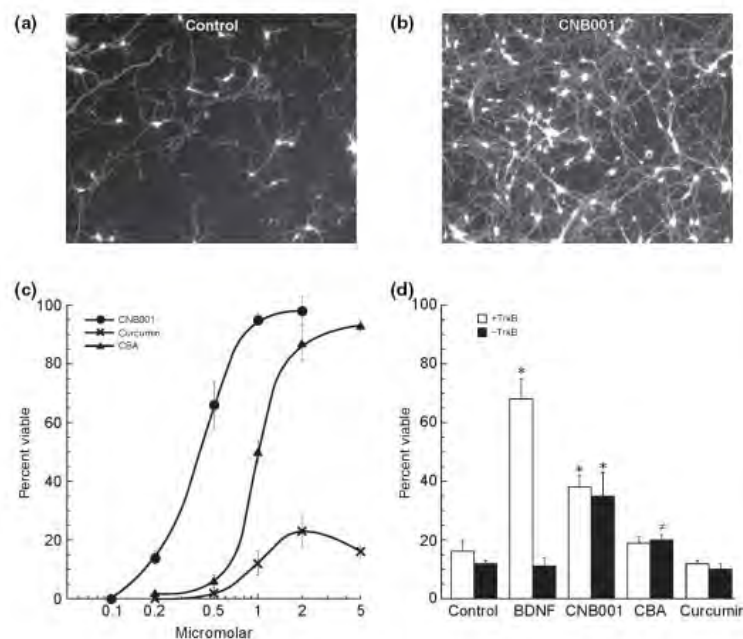


Curcumin derivative CNB-001

- **CNB001: Pyrazole derivative of Curcumin**
- **Cyclohexyl bisphenol A (CBA) + Curcumin = CNB001**
- Cyclohexyl bisphenol A (CBA): protective against A β and glutamate toxicity (Schubert and Liu, 2002, **US Patent No. 6,472,436B1**).
- CNB001 has improved EC₅₀ Value as compared to both parent compounds and is active in wide range of neuroprotective assays.



- Improved cellular viability
- Ability to protect nerve cells in the absence of Trophic factors



David Schubert

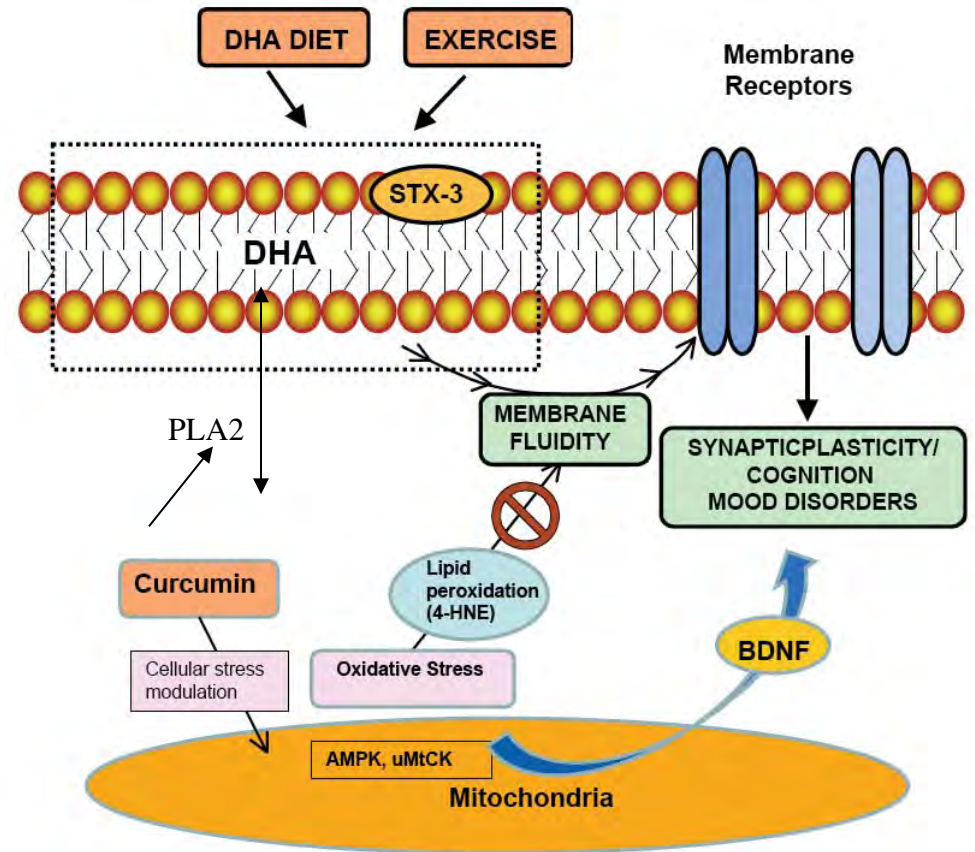
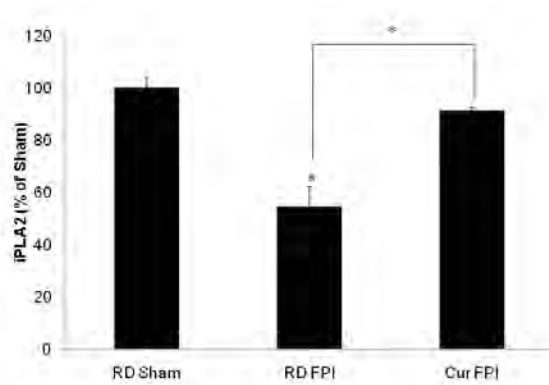
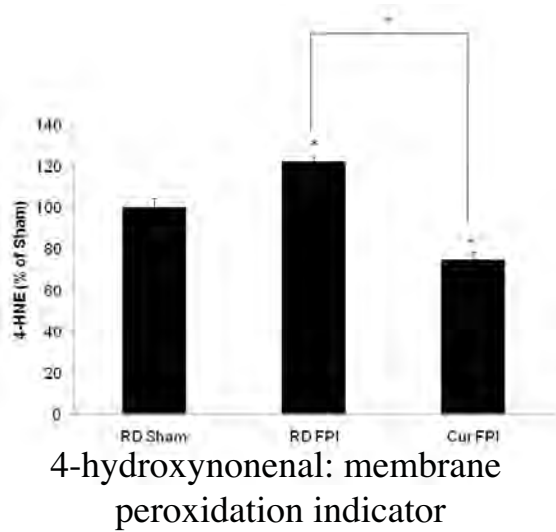
Laboratories of Cellular Neurobiology
The Salk Institute

Maher et al., 2008 Neurobiol Aging. 2008 Jul 16

Lin et al., 2008 J Neurochem. 105(4):1336-45.

J. Neurochem. (2008) **105**, 1336–1345

Curcumin reduces membrane damage by normalizing pathways associated with the metabolism of phospholipids



Curcumin reduces cerebral edema following TBI

- Aquaporins are a family of water membrane channels that permit selective bidirectional water flow in response to osmotic gradients (Yang et al, 2008).
- Curcumin blocked aquaporin-4 expression (Laid, et al., 2010)
- Effective during pre-treatment (75, 150 mg/kg) or 30 min post-treatment with 300 mg/kg

Dietary branched aminoacids (Cole et al., 2010)

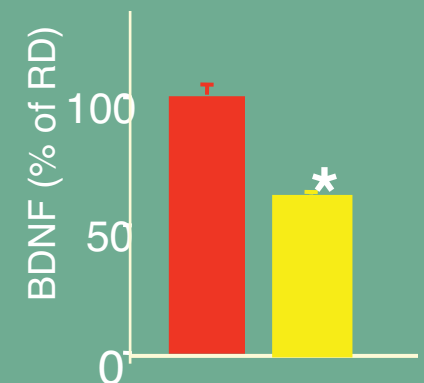
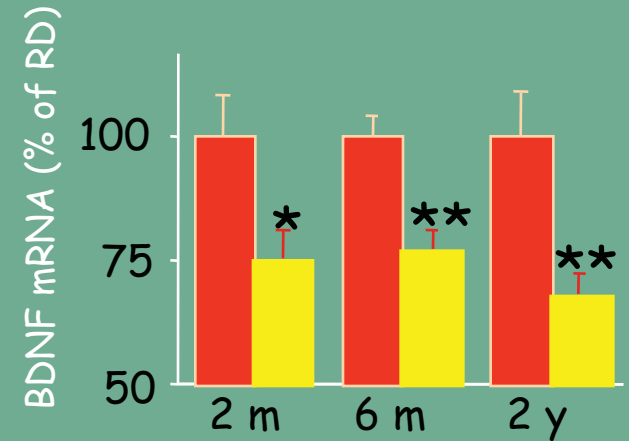
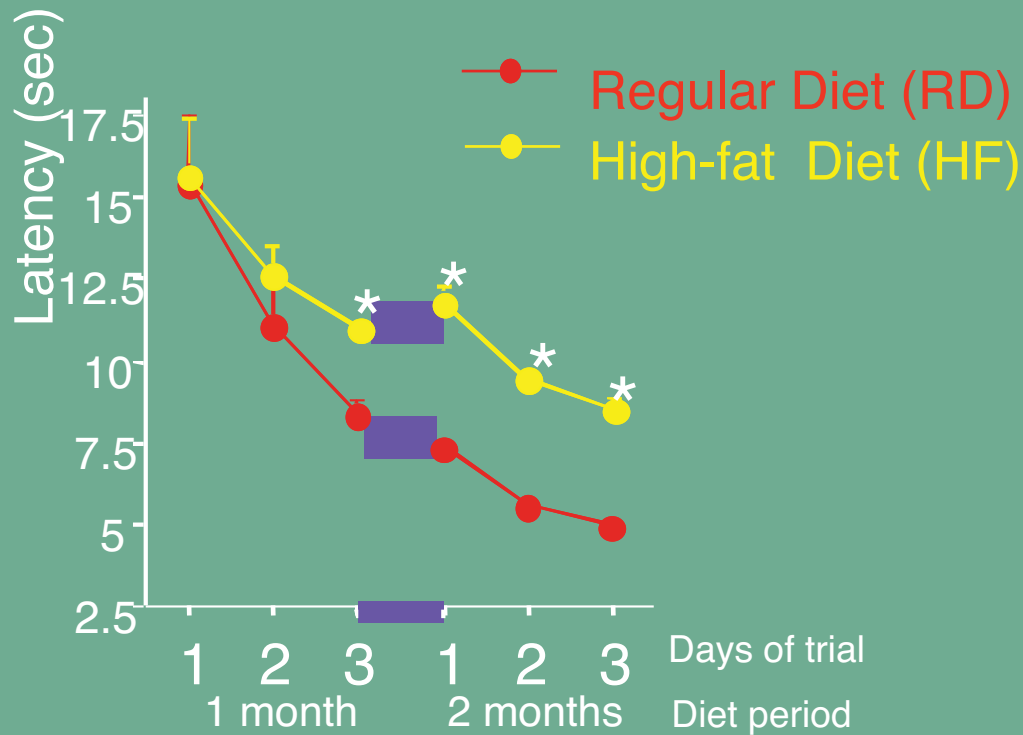
- TBI is associated with changes in neuronal excitability.
- Neuronal excitability partially depends on the excitatory (glutamate) and inhibitory (GABA) receptors.
- Cole et al show that BCAAs, in particular leucine, isoleucine, and valine, are important for the novo synthesis of glutamate, can restore injured-induced cognitive impairment.

What to avoid in the diet.....

- A diet high in saturated fat (38%) and sucrose is commonly consumed in industrialized societies: **HF** or “junk food diet”



A diet high in saturated fats (HF) reduces hippocampal BDNF and learning and memory capacity



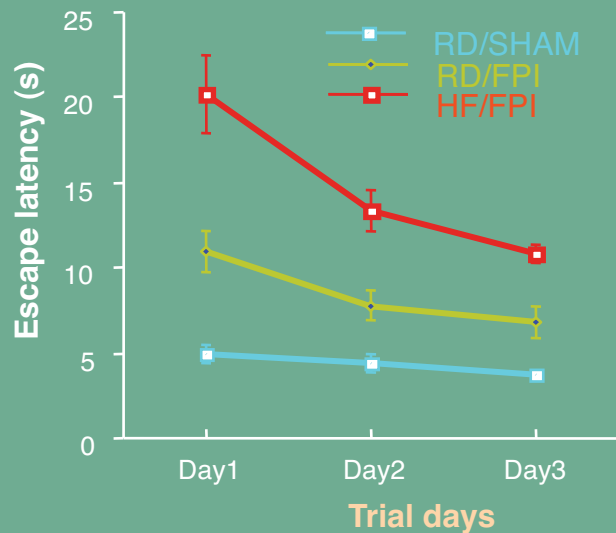
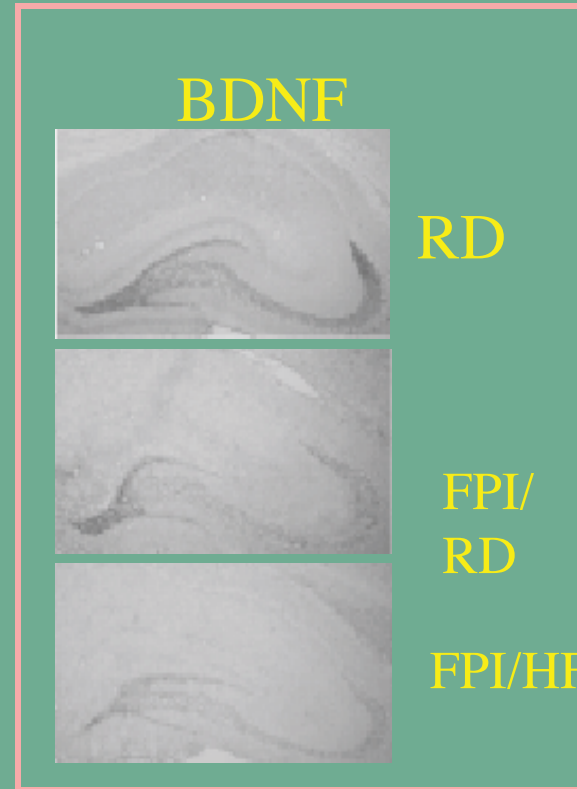
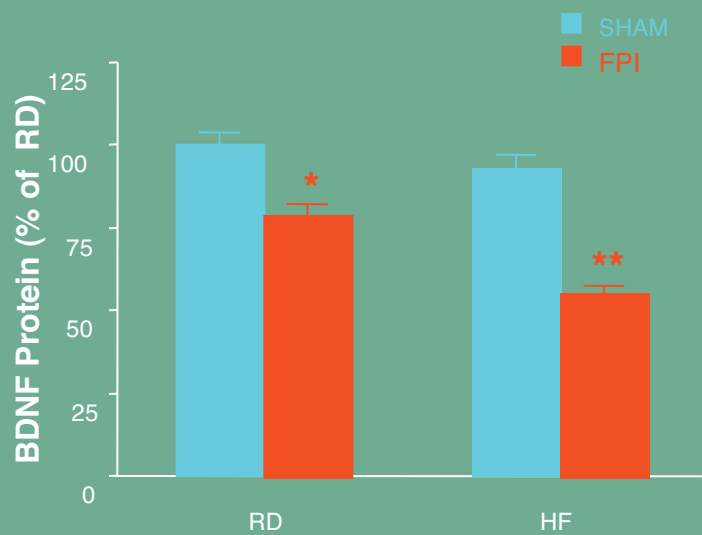
@changes relative to a low fat complex carbohydrate diet (LFCC or RD)

Molteni et al., Neuroscience, 2002

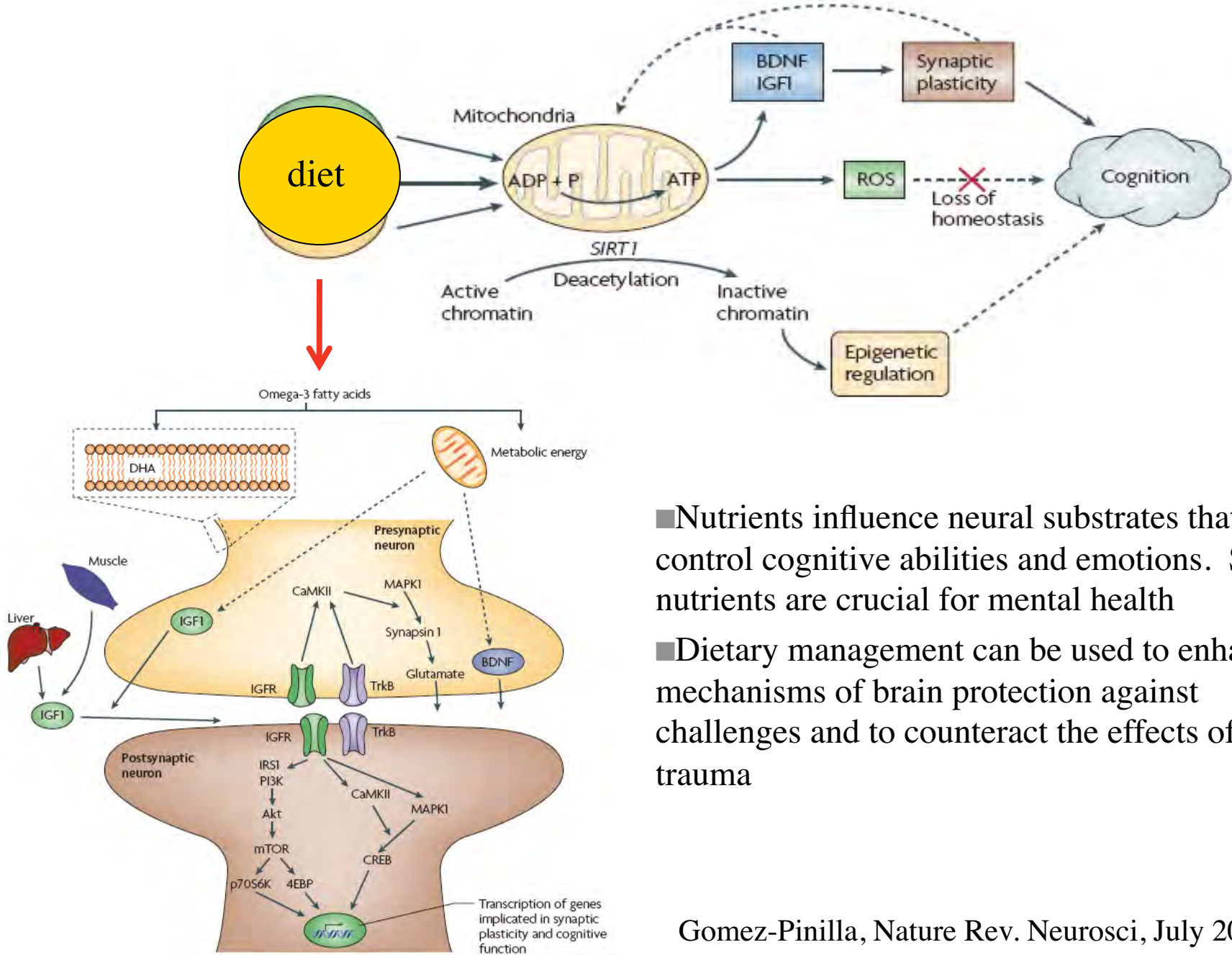
● HF: high fat (saturated/nonsaturated, 38% calories) sucrose diet

● RD: low fat (13% calories) complex carbohydrate (starch)

The HF diet potentiates the decrease in BDNF caused by FPI



Conclusion: Effects of diet on cognition and emotions



- Nutrients influence neural substrates that control cognitive abilities and emotions. Select nutrients are crucial for mental health
- Dietary management can be used to enhance mechanisms of brain protection against challenges and to counteract the effects of CNS trauma

Participants

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****thanks NIH/NINDS for sustained funding support!!**