

Hormones and Pain

Ron Rothenberg MD

Eicosanoids and Pain

- Eicosanoid hormones
- First hormones in evolution
- Produced by all cells
- Short half life - seconds
- Prostaglandins, Leucotrienes, Thromboxanes
- Control of Eicosanoids can control pain on cellular level

Prostaglandin E2 (PGE2)

- Inflammatory pain is caused by sensitization of peripheral and central nociceptive neurons.
- PGE2 sensitizes nociceptive neurons at both sites.

- Bar KJ et al. Changes in the effect of spinal prostaglandin E2 during inflammation: prostaglandin E (EP1-EP4) receptors in spinal nociceptive processing of input from the normal or inflamed knee joint. *J Neurosci*. 2004 Jan 21;24(3):642-51

PGE2 and joint pain

- PGE2 concentrations in synovial fluid may be correlated with the amount of pain
- Trumble TN et al. Correlation of prostaglandin E2 concentrations in synovial fluid with ground reaction forces and clinical variables for pain or inflammation in dogs with osteoarthritis induced by transection of the cranial cruciate ligament *Am J Vet Res.* 2004 Sep;65(9):1269-75

PGE2 in brain

- Produces hyperalgesia in medulla
- Heinricher MM et al. Prostaglandin E2 in the medial preoptic area produces hyperalgesia and activates pain-modulating circuitry in the rostral ventromedial medulla. *Neuroscience*. 2004;128(2):389-98.

PGE2 and brain

- PGE2 in medulla needed for neuropathic pain
- Mabuchi T et al. Membrane-associated prostaglandin E synthase-1 is required for neuropathic pain. *Neuroreport*. 2004 Jun 28;15(9) :1395-8.

PGE2 and RA

- PGE2 is needed for pathogenesis and joint damage of RA
- PGE2 is responsible for joint pain of RA

- McCoy JM et al. The role of prostaglandin E2 receptors in the pathogenesis of rheumatoid arthritis. *J Clin Invest.* 2002 Sep;110(5):651-8.

Where does PGE2 come from?

- Arachadonic Acid
 - Fats from Omega 6 pathway
 - Pre-formed in Animal fat
- Control with diet, Omega 3's and NSAIDS

PGE2, pain, COX

- Thoracic surgical wounds increase pain-related behavior and CSF and tissue PGE2 levels, all of which can be attenuated by oral cyclooxygenase inhibitors.
- Kroin JS et al. Upregulation of cerebrospinal fluid and peripheral prostaglandin E2 in a rat postoperative pain model. *Anesth Analg*. 2006 Aug;103(2):334-43

Vitamin D

CRP

Red inhibits
Yellow activates

Resveratrol
EPC's

Unified Theory
of Wellness:
Chronic
Inflammation Is
the Cause and
the Effect of the
Diseases of
Aging



p53

Angio-
tensin II

EPA, DHA
from Fish
OIL

Pain

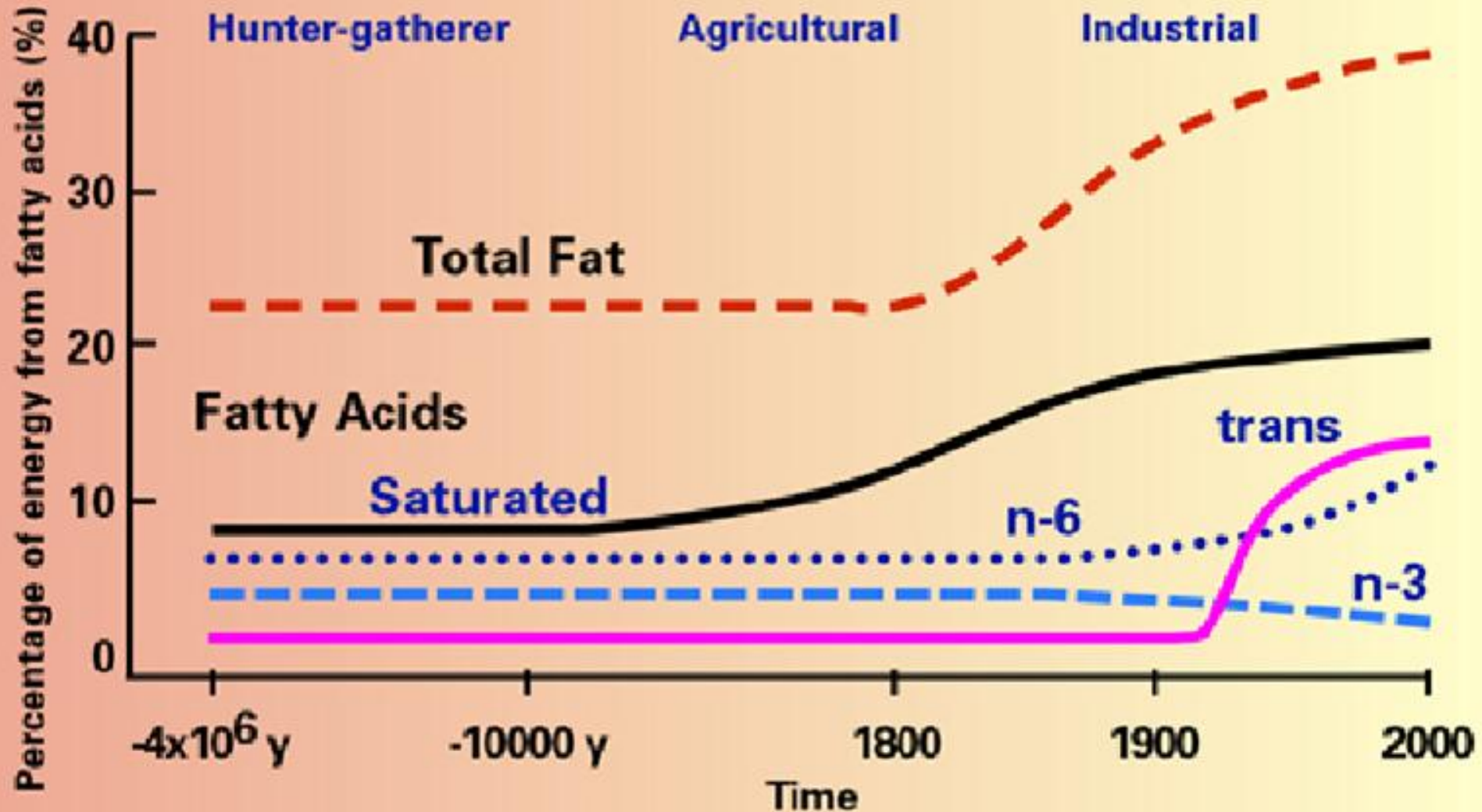
PGE2:
Pain
Cancer
Skin aging

TXA2
Athero-
sclerosis

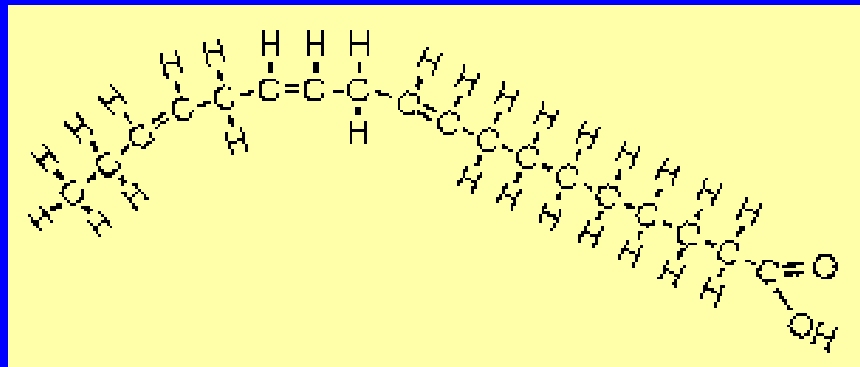
Nuclear Factor Kappa Beta controls COX and LOX

- Stress
- Depression
- Adipose
- Antioxidants
- Exercise
- Omega 3's
- Nutrition – insulin control
- Homocysteine control
- Youthful hormone levels
- Omega3/Omega6

Fats through the ages



- Fatty acid nomenclature
- Fatty acids can be identified by 3 important characteristics (in this order).
 - 1. Chain length (number of carbons)
 - 2. The number of carbon-carbon double bonds.
 - 3. The location (starting from the methyl end) of the first double bond.
- 18:3 n-3 (or w3) for linolenic acid



n-3, n-6 and Inflammation

- EPA and DHA inversely associated with TNF and CRP
- ALA not associated with inflammatory markers
- The higher the intake of n-6 the more important n-3 for anti-inflammation
- Pischon T et al. Habitual dietary intake of n-3 and n-6 fatty acids in relation to inflammatory markers among US men and women. *Circulation*. 2003 Jul 15;108(2):155-60.

THE OMEGA-6 PATHWAY

THE OMEGA-3 PATHWAY

D6D decreased
 Age \geq 30
 $<$ 6 months
 viral infections
 Trans fats
 Short n-3
 Long n-3
 Cortisol

Linoleic acid (LA)
18:2n-6
(Soy, corn, cottonseed, safflower oils)
 Sunflower, peanut

Alpha-Linolenic acid
ALA=(LNA) 18:3n-3
(Flax oil, grains, green vegetables)

LA and LNA compete for D6D

Delta-6 Desaturase (D6D)

Delta-6 Desaturase (D6D)

High carb diets which cause increased insulin levels increase AA

Gamma-linolenic acid (GLA) 18:3n-6
(Evening primrose, borage, black currant oils)
 Slow cooked oatmeal Breast milk

Octadecatetraenoic acid 18:4n-3

Insulin Activates D5D

Good Eicosinoids

Elongase enzyme

Elongase enzyme

Glucagon EPA inhibits D5D

SERIES 1 PROSTAGLANDINS
 TXA₁ PGE₁
 PGE_{1a} PGD₁

Dihomo-gamma-linolenic acid (DGLA) 20:3n-6

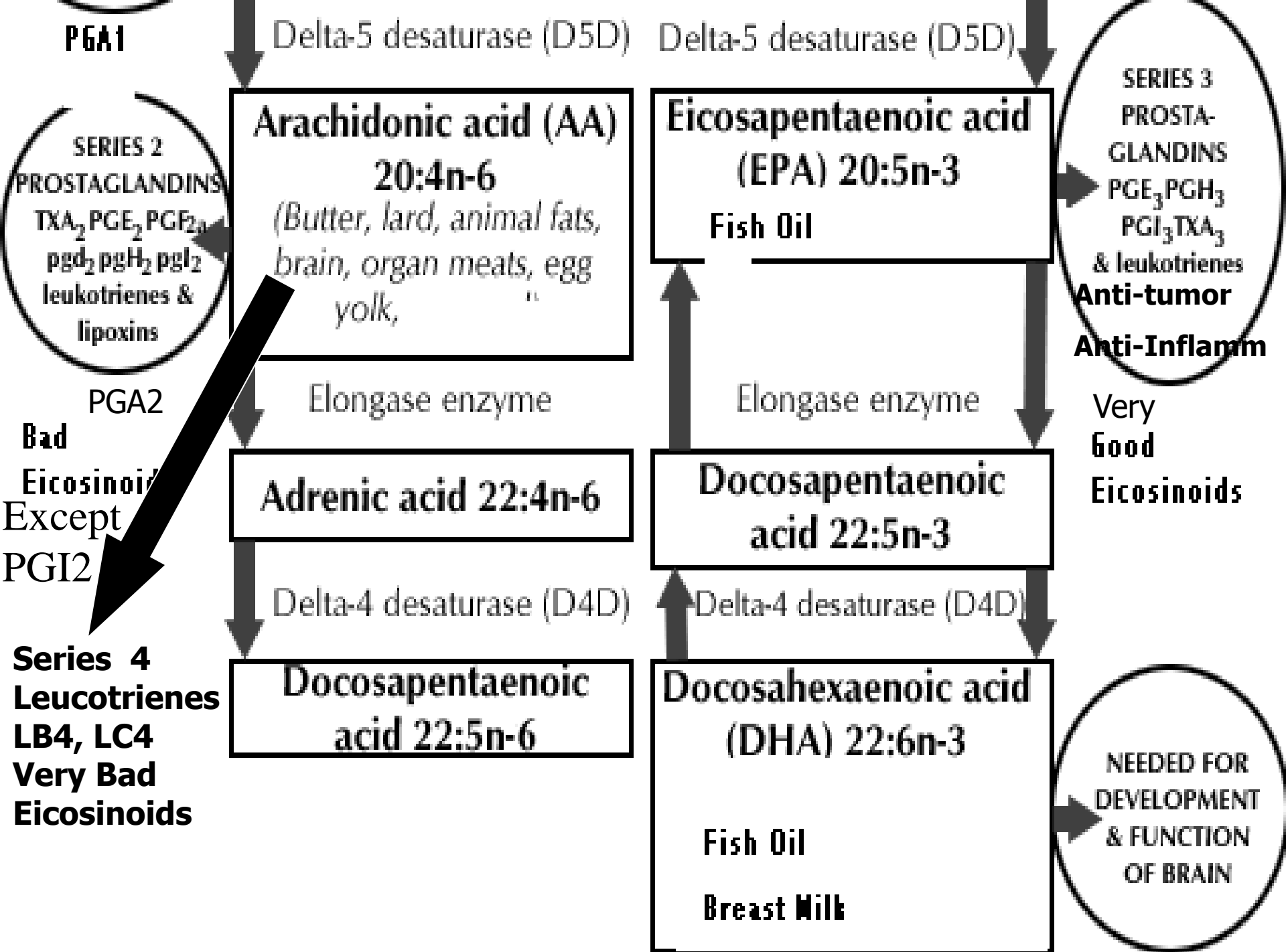
Eicosatetraenoic acid 20:4n-3

PGA1

Delta-5 desaturase (D5D)

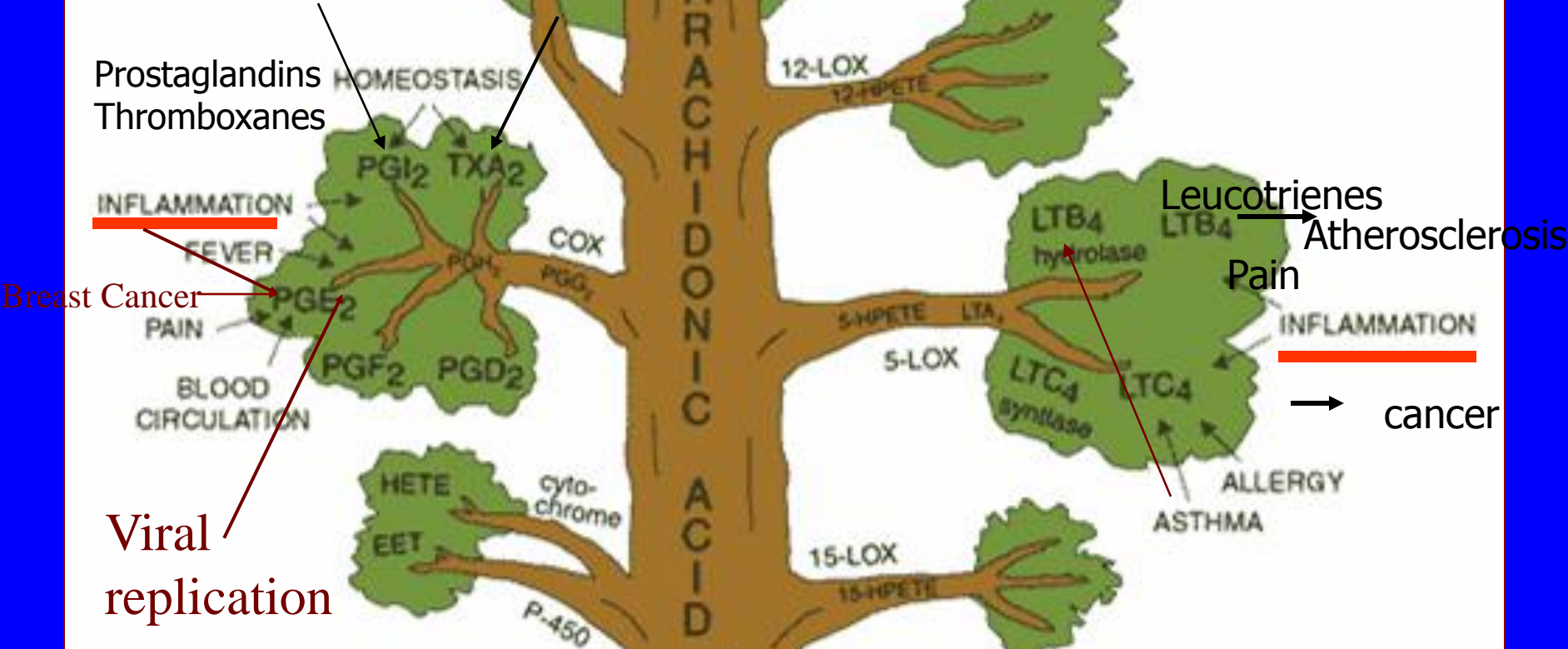
Delta-5 desaturase (D5D)





COX, LOX are key enzymes for eicosanoid synthesis

Prostacyclin, Vasodilation, Vasoconstriction, Atherosclerosis. Plaque formation



Breast Cancer
Viral replication

Leucotrienes
Atherosclerosis
Pain
Inflammation
cancer

PGI2, PGA2 cytoprotective
Blocked by COX2 inhibition
Not all "bad" Eicosanoids are bad

Lipoxins	LTB4
Hydroxylated	PGE2
Fatty acids	Pain
	Inflammation

Good and Bad Eicosanoids

- **Series 1 & 3**
- **(including PGI₂)**

- **Increased vasodilation**
- **Decreased pain**
- **Increased endurance**
- **Enhanced immune system**
- **Increased oxygen flow**
- **Decrease in cellular proliferation**
- **Prevents platelet aggregation**
- **Dilates airways**
- **Decreases inflammation**

- **Series 2 and 4**
- **(except PGI₂)**

- **Increased vasoconstriction**
- **Increased pain**
- **Decreased endurance**
- **Immune system suppression**
- **Decreased oxygen flow**
- **Increases cellular proliferation**
- **Creates platelet aggregation (clotting)**
- **Constricts airways**
- **Increases inflammation**

n-6/n-3 ratio?

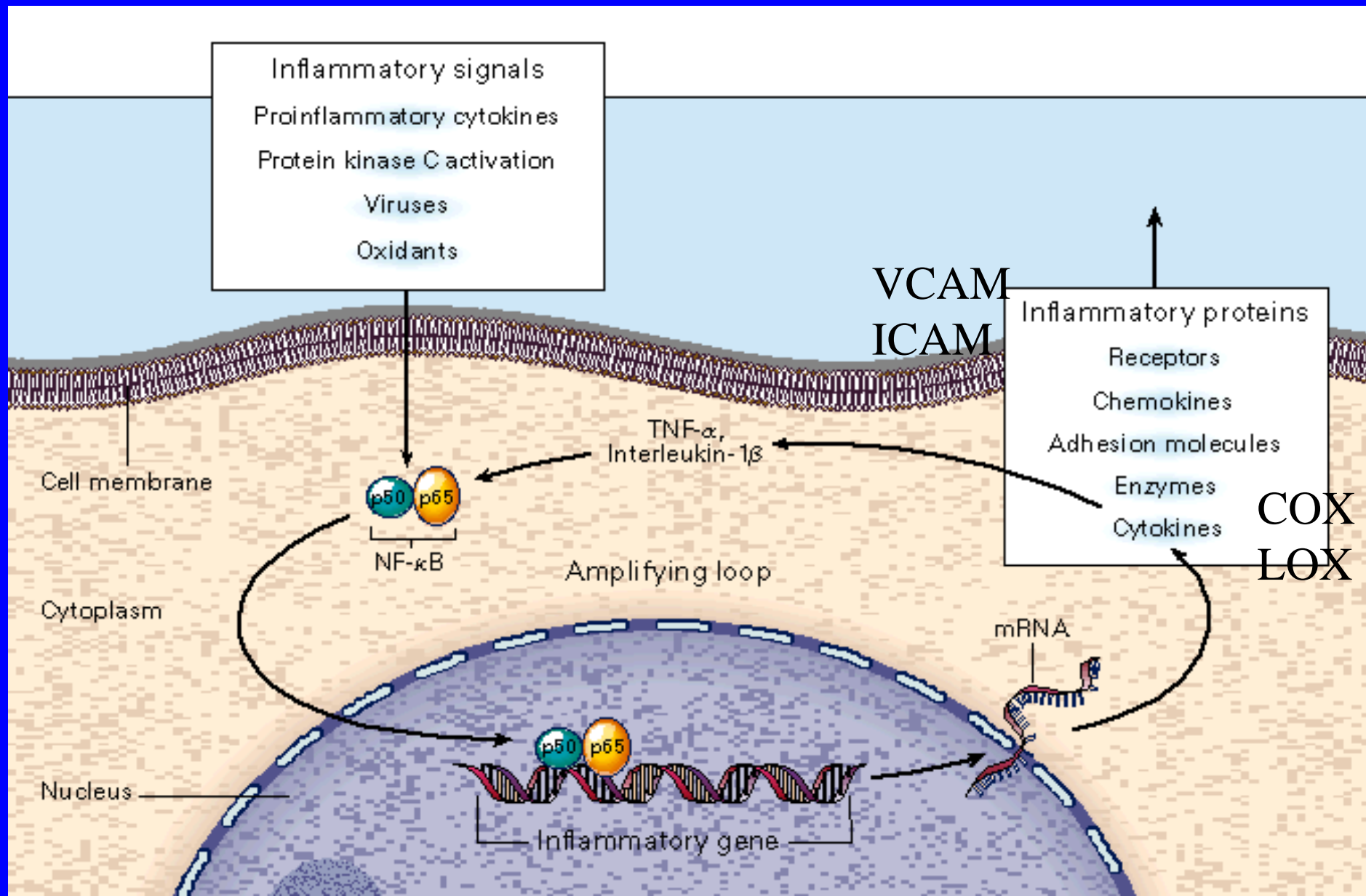
- Arachidonic/EPA ratio in serum
- Greenland Eskimos 0.7
- Japanese 1.5
- Americans 10-20
- ADHD 20-30

- Goal 1.5-3.0

NF-kB

- Nuclear Factor Kappa Beta is central to inflammation, pain, atherosclerosis, cancer, cognitive function and more
- PGE2 can be controlled by NFkB control
- Cytokine amplification pathway
 - IL6, IL1beta, TNF alpha
- Lee KM et al. Spinal NF-kB activation induces COX-2 upregulation and contributes to inflammatory pain hypersensitivity. *Eur J Neurosci*. 2004 Jun;19(12):3375-81.

Positive regulatory loop



Vitamin D

CRP

Red inhibits
Yellow activates

**Resveratrol
EPC's**

Unified Theory
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EPA, DHA from Fish OIL

Pain

PGE2:
Pain
Cancer
Skin aging

**TXA2
Athero-sclerosis**

Cytokines and cancer pain

- Cancer symptoms including pain, fatigue, sleep disturbance, cognitive dysfunction and affective symptoms are secondary to NFκB expression
- Lee BN et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. *Neuroimmunomodulation*. 2004;11(5):279-92.

Omega 3 and dysmenorrhea

- 2.0 grams Omega 3 vs placebo
- CONCLUSIONS: This study suggests that dietary supplementation with omega-3 fatty acids has a beneficial effect on symptoms of dysmenorrhea in adolescents.
P <.004
- Harel Z et al. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents.*Am J Obstet Gynecol.* 1996 Apr;174(4):1335-8.

Omega 3 and RA

- Placebo controlled, double blind
- 130 mg/kg/day of omega 3 fatty acids or 9 capsules/day of corn oil.
 - 130mg x 70kg = 9.1 g of omega 3 fatty acids
- Fish oil: there were significant decreases in number of tender joints ($P < 0.0001$)
- Duration of morning stiffness ($P = 0.008$)
- Physician's and patient's evaluation of global arthritis activity ($P = 0.017$ and $P = 0.036$, respectively)
- Physician's evaluation of pain ($P = 0.004$)
- IL1 decreased
- Can discontinue NSAIDS without disease flare
- Kremer JM et al. Effects of high-dose fish oil on rheumatoid arthritis after stopping nonsteroidal antiinflammatory drugs. Clinical and immune correlates. *Arthritis Rheum.* 1995 Aug;38(8):1107-14.

Omega 3, pain and brain

- Omega 3 decrease pain of pro-inflammatory eicosanoid and cytokine production by peripheral tissues.
- Omega 3's have also been shown to inhibit eicosanoid production in glial cells, block voltage-gated sodium channels (VGSCs), inhibit neuronal protein kinases and modulate gene expression
- Shapiro H et al. Could n-3 polyunsaturated fatty acids reduce pathological pain by direct actions on the nervous system? *Prostaglandins Leukot Essent Fatty Acids*. 2003 Mar;68(3):219-24.

California HealthSpan experience

- “Inuit” dose of Omega 3’s – 8 grams per day
- Limit Omega 6’s (safflower oil etc. in diet)
- Control Insulin levels with Zone diet
- More effective than any NSAID
- Improves many other parameters of Q o L
 - Triglycerides cut in half
 - Depression improved
 - Cognitive function increased
 - Risk of sudden death and many cancers decreased based on current literature

Gender differences in pain

- Greater pain sensitivity in females
- More postop pain in women
- Women more at risk for pain syndromes
- Greater neuropathic pain in women
- Fillingim R et al. Sex, gender, and pain: a review of recent clinical and experimental findings. *J Pain*. 2009 May;10(5):447-85.

Sex, Hormones and Pain

- Pre-pubertal boys and girls – same migraine incidence
- Post puberty – female 2x
- “HRT” Increased pain (without Test)
- “OCP” Increased pain
- Male to Female transsexual – More pain
- Female to Male transsexual – Less Pain

Opioid-induced endocrinopathy.

- Pituitary: Decreased FSH, LH, GH
- Testicles: Decreased Test production
- Adrenals: Decreased cortisol and DHEA
- Men: Decreased Testosterone
- Women: Menstrual Irregularities, Decreased Testosterone, Estrogens, Progesterone

Opioid-induced endocrinopathy.

- Decreased levels of
 - Testosterone
 - Estradiol, Progesterone,
 - Growth hormone
 - DHEAS,
 - Cortisol

- Colameco S et al. Opioid-induced endocrinopathy.
J Am Osteopath Assoc. 2009 Jan;109(1):20-5.

Opioid endocrinopathy

- Long term treatment of chronic pain with opioids cause hormonal abnormalities
- Hormone replacement indicated
- Stopping or decrease of opioid can reverse abnormalities

- Rhodin A et al. Opioid endocrinopathy: a clinical problem in patients with chronic pain and long-term oral opioid treatment. *Clin J Pain* 2010 Jun;26(5) :374-80

OPIAD

- Use of long-acting opioid preparations results in a syndrome of **opioid induced androgen deficiency (OPIAD)** in men with chronic pain
 - Decreased levels of testosterone,
 - decreased libido,
 - erectile dysfunction,
 - fatigue
 - depressed mood
 - hot flashes.
- Low testosterone levels decrease nociceptive threshold in animal models and men
- Mazer et al. Opioid Induced Androgen Deficiency in Men (OPIAD): An Estimate of the Potential Patient Population in the U.S. and Canada. *American Pain Society*, 2004

Intrathecal opioids and hormones

- Decreased T in men and women
 - Hypogonadotropic hypogonadism
 - Sexual function increased with TRT
- Low GH in men and women

- Abs R Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab.* 2000 Jun;85(6):2215-22.

Testosterone and pain

- Testosterone increases pain threshold
- Decreases inflammatory cytokines
- Opioid treatment decrease testosterone levels
- Testosterone replacement therapy (TRT) improves pain and Quality of Life in men and women
- TRT is safe

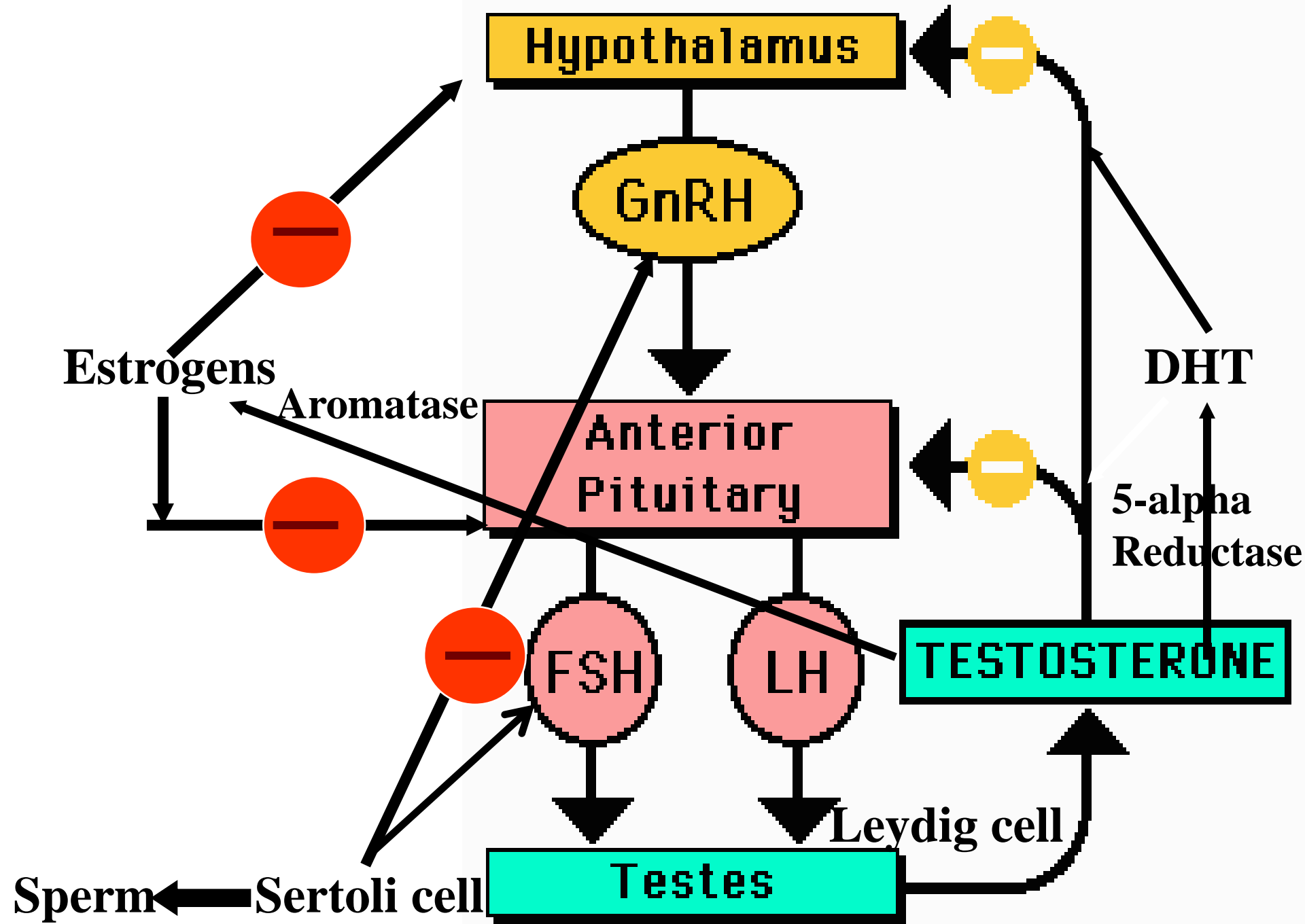
T and pain and Sparrows

- T involved in aggressive behavior and risk of injury and risk of pain
- This could be distracting in fighting for territory, females
- Skin nociception was quantified by foot immersion into a hot water bath, a benign thermal stimulus.
- Males treated with exogenous testosterone left their foot longer in hot water than control birds.
- Conversely, males in which the physiological actions of testosterone were pharmacologically blocked withdrew their foot faster than control birds.
- Hau M et al. Testosterone reduces responsiveness to nociceptive stimuli in a wild bird. *Horm Behav.* 2004 Aug;46(2):165-70.

Opioids and T

- Naturally occurring opiates (endorphins) diminish testosterone levels by inhibiting both hypothalamic gonadotrophin releasing hormone production and testicular testosterone synthesis.
- Chronic opioid treatment
- Decreased T and Free T, LH, GnRH
- Erectile dysfunction

- Daniell HW et al. Hypogonadism in men consuming sustained-action oral opioids. *J Pain*. 2002 Oct;3(5):377-84.



Females, opioids, pain, T

- Females with low T (< 15 ng/dl) on opioids for chronic pain
- 5 gms 1% T x 30 days
- 71.0% reported increase in libido, pain control, endurance, and energy.
- 50% reported a decrease in daily opioid requirement.
- No side-effects were observed.
- Females with severe persistent pain who are treated with opioids develop hypotestosteronemia, and they benefit from testosterone replacement.
- Tennant et al. Hypotestosteronemia and testosterone replacement in females with severe, persistent pain. *American Pain Society, 2004*

TRT improves angina pain

- Improves causes of angina
- Raises pain threshold?

- Malkin CJ et al. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart*. 2004 Aug;90(8):871-6.

TRT- less anxiety and pain in rats

- T has anxiety reducing and cognitive enhancing properties in animals and humans
- T administration produced analgesia and enhanced affect and cognitive performance of adult male rats.
- Frye CA et al. Testosterone increases analgesia, anxiolysis, and cognitive performance of male rats. *Cogn Affect Behav Neurosci*. 2001 Dec;1(4):371-81.

2D:4D



- More pain tolerance in females who had greater difference in 2D:4D
- Keogh E. Can a sexually dimorphic index of prenatal hormonal exposure be used to examine cold pressor pain perception in men and women? : *Eur J Pain*. 2006 Apr 4

T replacement and inflammation

- Less inflammatory cytokines TNF, IL-1beta
- More anti-inflammatory cytokines IL-10
- Lower total cholesterol

- Malkin CJ et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men *J Clin Endocrinol Metab.* 2004 Jul;89(7):3313-8.
- Malkin CJ et al. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart.* 2004 Aug;90(8):871-6.

Inflammation and sex hormone metabolism

- Autoimmune disease higher in females than males
- In both sexes adrenal hormones are low (DHEA and cortisol)
- Androgens: Anti-inflammatory
- Estrogens: Pro-inflammatory
- Local metabolism may determine pro or anti-inflammation
- Schmidt M et al. Inflammation and sex hormone metabolism. *Ann N Y Acad Sci.* 2006 Jun;1069:236-46.
- Schmidt M et al. Androgen conversion in osteoarthritis and rheumatoid arthritis synoviocytes--androstenedione and testosterone inhibit estrogen formation and favor production of more potent 5alpha-reduced androgens. *Arthritis Res Ther.* 2005;7(5):R938-48.

Hormones and RA

- Estrogens enhance humoral immunity, and androgens and progesterone are natural immune suppressors.
- Low testosterone, DHT and DHEA and reduced androgen:estrogen ratio detected in male and female RA patients.
- Androgen treatment improves male and female patients
- Cutolo M Sex hormone adjuvant therapy in rheumatoid arthritis *Rheum Dis Clin North Am.* 2000 Nov;26(4):881-95.

Hormones and RA

- Testosterone lower
- Estradiol higher
- Higher Estradiol, more inflammation
- DHEAS lower

- Tengstrand B et al. Abnormal levels of serum dehydroepiandrosterone, estrone, and estradiol in men with rheumatoid arthritis: high correlation between serum estradiol and current degree of inflammation. *J Rheumatol.* 2003 Nov;30(11):2338-43

Rheumatic Autoimmune Disease (RAD) and T in Men

- Low frequencies of RADs in men
- High frequencies in patients with untreated hypogonadism ($P < 0.001$) and low serum testosterone levels ($P = 0.0005$).
- Jimenez-Balderas FJ et al. High frequency of association of rheumatic/autoimmune diseases and untreated male hypogonadism with severe testicular dysfunction.
Arthritis Res. 2001;3(6):362-7. 2001 Sep 12.

T and ankylosing spondylitis

- Increased LH
- Decreased T
- Decreased T/E ratio
- Improved with HCG treatment

- Tapia-Serrano R et al. Testicular function in active ankylosing spondylitis. Therapeutic response to human chorionic gonadotrophin. *Rheumatol.* 1991 Jun;18(6):841-8.

T and osteoarthritis

- Positive association with serum testosterone at all tibial cartilage sites
- Cicuttini FM et al. Factors affecting knee cartilage volume in healthy men. *Rheumatology* (Oxford). 2003 Feb;42(2):258-62.

California HealthSpan Experience with TRT

- Anti-inflammatory effects, often restoring lifestyle to formerly active patients
- Decreased pain in osteo and RA
- Increases libido and sexual function
- Increased muscle and bone, decreased fat
- Improved Energy, mood and Q o L
- PSA values decrease more often than increase
- Easily managed and rare side effects in women
- Improved CRP

DHEA and pain

- DHEAS was negatively associated with musculoskeletal pain in menopausal women

- Finset A Musculo-skeletal pain, psychological distress, and hormones during the menopausal transition *Psychoneuroendocrinology*. 2004 Jan;29(1):49-64.

GH and musculoskeletal pain

- Decreased growth hormone secretion, leading to a state of **adult growth hormone deficiency**, may occur in the setting of chronic inflammatory disease, chronic corticosteroid use, and fibromyalgia
- GHRT can improve chronic pain

- Bennett R Growth hormone in musculoskeletal pain states. *Curr Rheumatol Rep*. 2004 Aug;6(4):266-73.

Fibromyalgia Definition

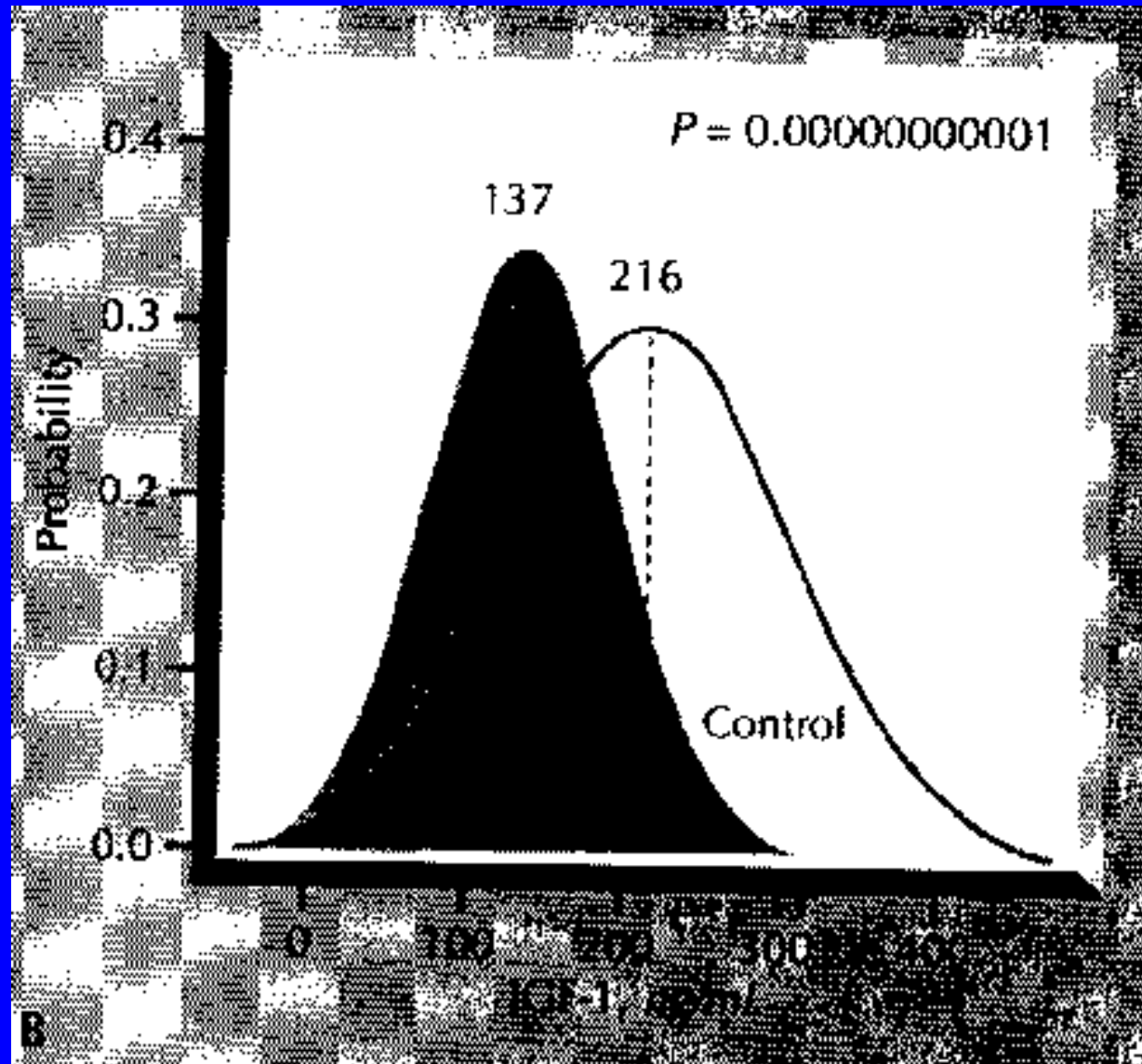
National FM Association

- Fibromyalgia is an increasingly recognized chronic pain illness
- Widespread musculoskeletal aches, pain and stiffness
- Soft tissue tenderness
- General fatigue and sleep disturbances
- The most common sites of pain include the neck, back, shoulders, pelvic girdle and hands
- Any body part can be involved
- Fibromyalgia patients experience a range of symptoms of varying intensities that wax and wane over time

GH and Fibromyalgia

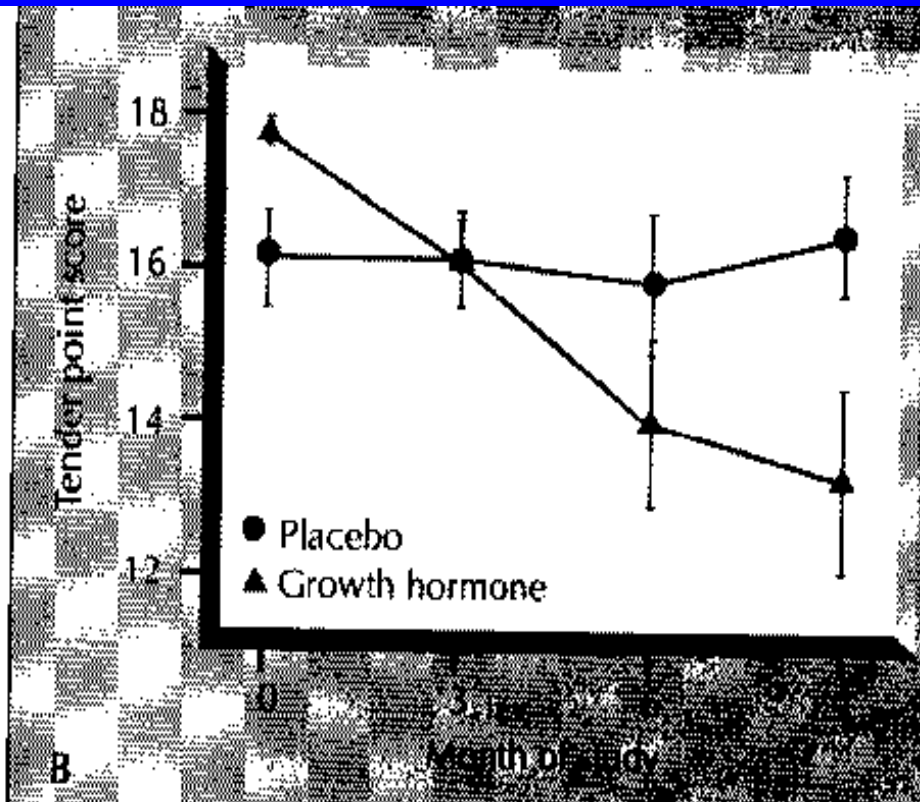
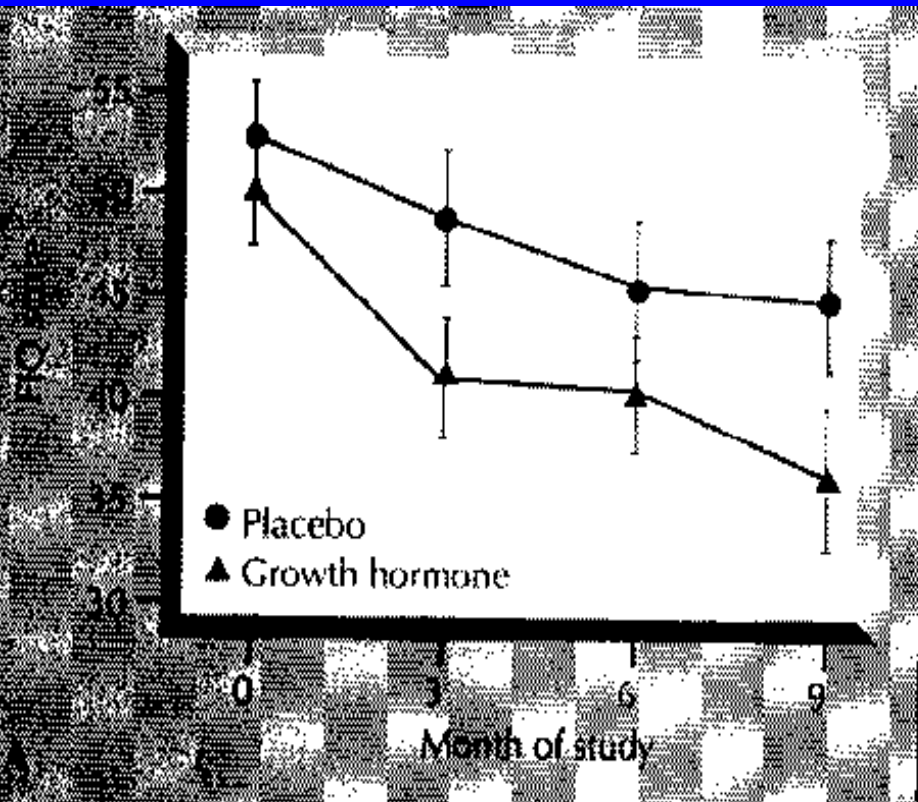
- Placebo Controlled, double blind
- Women with Fibromyalgia and low IGF-1
- Women with fibromyalgia and low IGF-1 levels experienced an improvement in their overall symptomatology and number of tender points after 9 months of daily growth hormone therapy.
- This suggests that a secondary growth hormone deficiency may be responsible for some of the symptoms of fibromyalgia.
- Bennett RM et al. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia *Am J Med.* 1998 Mar;104(3):227-31.

IGF-1 in FM vs. Control



■ Bennett RM
et al.

FM Impact Questionnaire and Trigger Points



■ Bennett RM et al. A randomized, double-blind, placebo-controlled study of growth hormone in the treatment of fibromyalgia *Am J Med.* 1998 Mar;104(3):227-31.

GH and FM

- Decreased GH secretion in patients with FM could contribute to symptoms:
- Reduced exercise tolerance, impaired vitality, cold intolerance, muscle weakness, and a feeling of social isolation,
- Beneficial effect of treatment with GH in patients with FM has been observed
- FM resembles GH deficiency
- Leal-Cerro A The growth hormone (GH)-releasing hormone-GH-insulin-like growth factor-1 axis in patients with fibromyalgia syndrome.
J Clin Endocrinol Metab. 1999 Sep;84(9):3378-81.

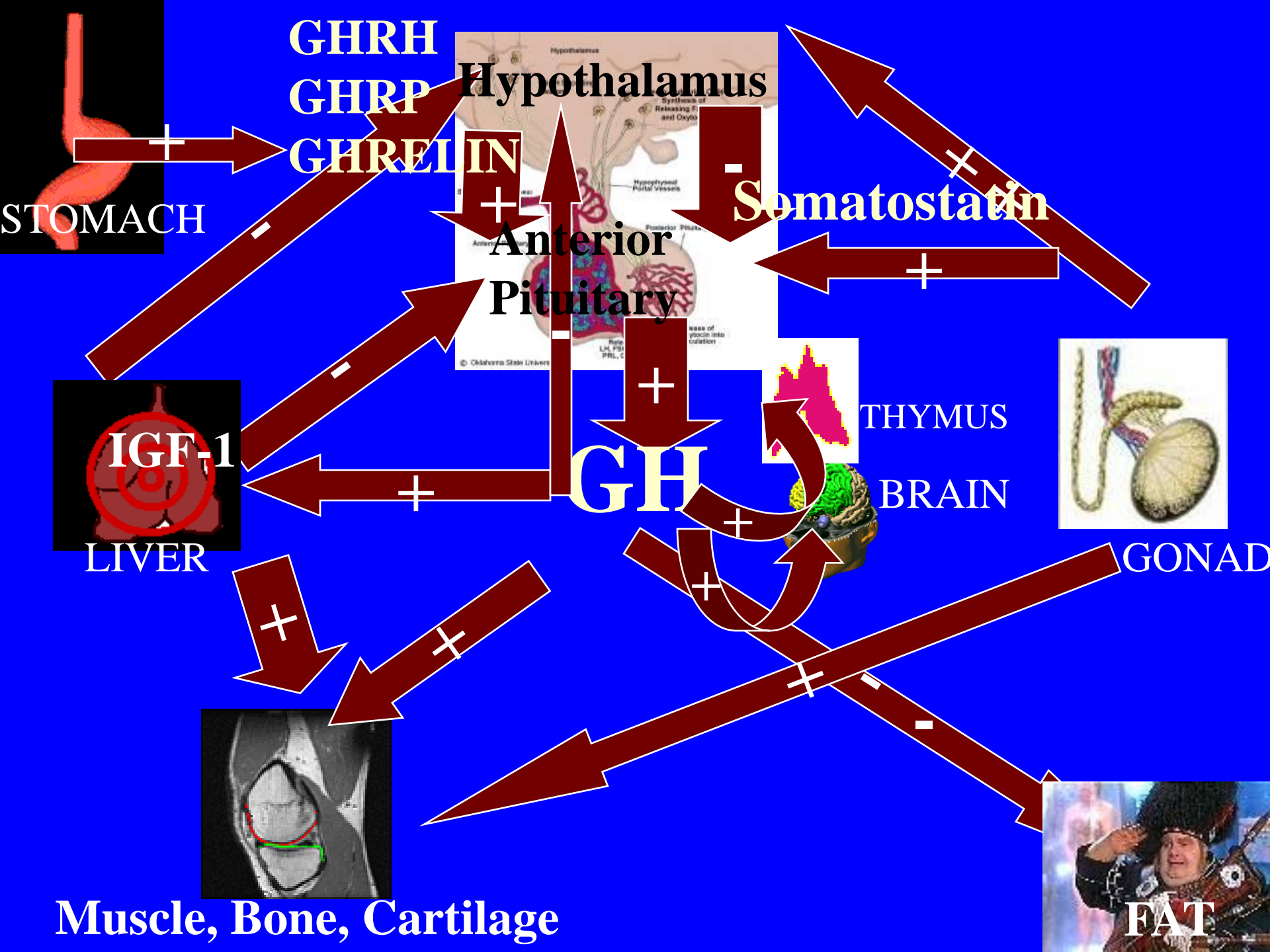
Adult GH deficiency resembles FM

- Low energy
- Poor general health
- Reduced exercise capacity
- Muscle weakness
- Cold intolerance
- Impaired cognition
- Decreased lean body mass

Adult GH Deficiency and FM

- GH needed for muscle homeostasis
- GH needed for repair of muscle microtrauma
- Treatment of GH deficiency improves FM symptoms
 - Pain
 - Depression, Low self esteem
 - Dyslipidemia
 - Cognitive function
 - Stroke Volume
 - Exercise capacity and muscle strength

- FM patients have an abnormal sleep pattern involving stages 3 and 4 of non REM sleep
- Moldofsky H, Scarisbrick P, England R, Smythe H: Musculoskeletal symptoms and non-REM sleep disturbance in patients with "fibrositis syndrome" and healthy subjects. *Psychosom Med* 1975, 37:341-351.



GHRH

GHRP

GHRELIN

Hypothalamus

Anterior Pituitary

Somatostatin

GH

THYMUS

BRAIN

GONAD

IGF-1

LIVER

Muscle, Bone, Cartilage

FAT

STOMACH

GH and Crohn's Disease

- Significant improvement in patients treated with GH
- Side effects minor and transitory
- **Slonim AE et al. A preliminary study of growth hormone therapy for Crohn's disease. *N Engl J Med* 2000 Jun 1;342(22):1633-7**

California HealthSpan Experience with GHRT

- Dramatic anti-inflammatory effect sometimes seen
- Increased muscle, bone and decreased fat
- Improved pain syndromes, depression, Q of L
- Side effects minor and easy to manage
- Improved CRP

Melatonin

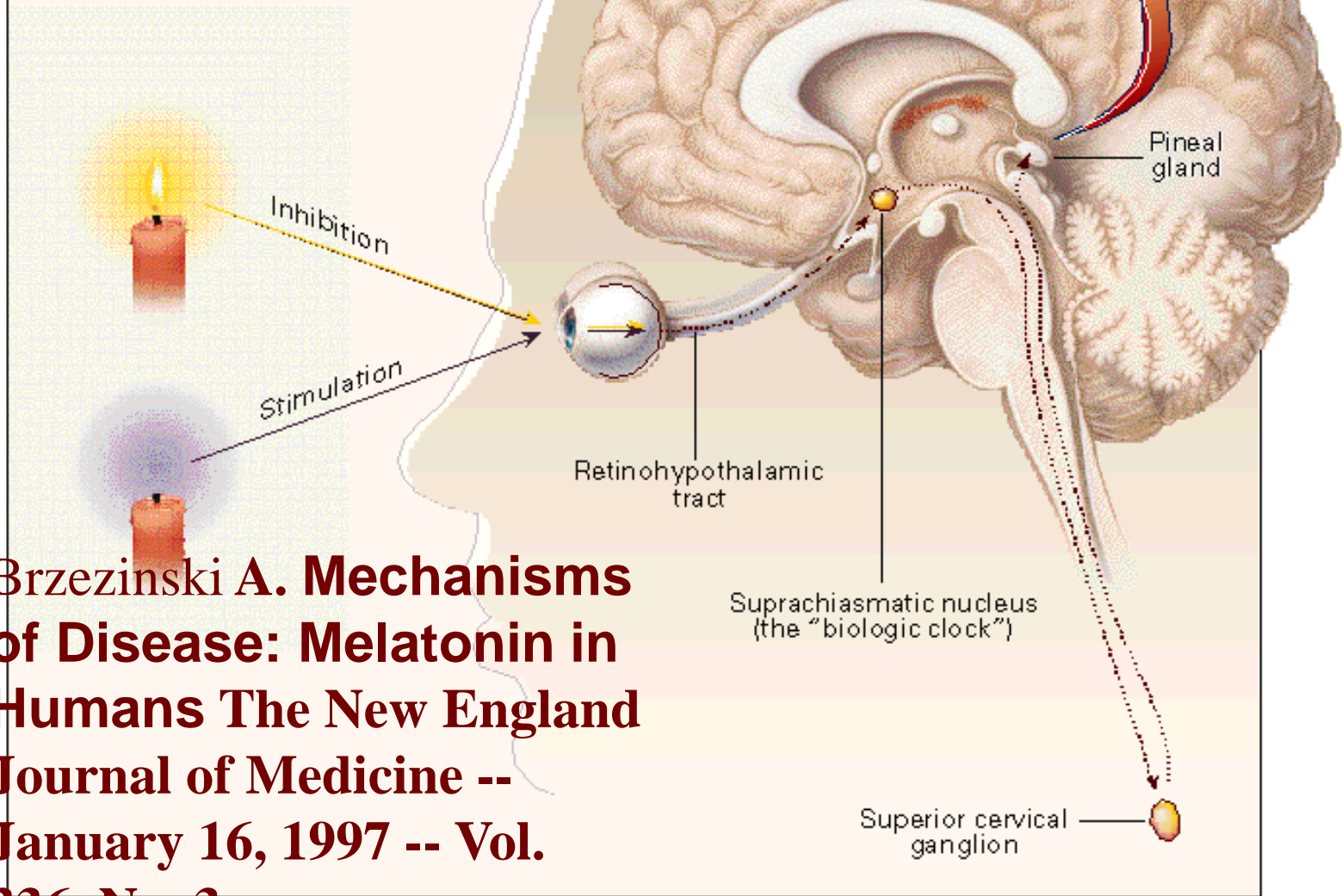
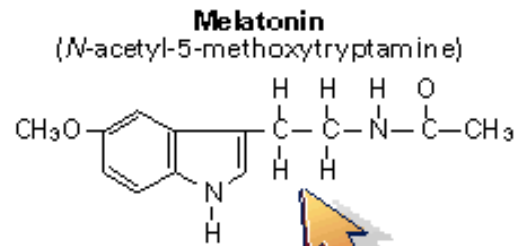
- Melatonin levels decreased in migraine and cluster headaches
- Improved pain in migraine and cluster headaches with treatment

- Peres MF et al. Potential therapeutic use of melatonin in migraine and other headache disorders. *Expert Opin Investig Drugs*. 2006 Apr;15(4):367-75.

Melatonin

- Anti-inflammatory
- Toxic free radical scavenging
- Reduction of pro-inflammatory cytokines
- GABA and opioid analgesia potentiation
- Similarity in chemical structure to indomethacin.
- Restores circadian rhythm
- Pang CS et al. Effects of melatonin, morphine and diazepam on formalin-induced nociception in mice. *Life Sci.* 2001 Jan 12;68(8):943-51.

Tryptophan → Serotonin →



Brzezinski A. Mechanisms of Disease: Melatonin in Humans The New England Journal of Medicine -- January 16, 1997 -- Vol. 336, No. 3

Melatonin - N-acetyl-5-methoxytryptamine

- Secreted by pineal gland
- Produced in darkness, suppressed by light
- Levels decline with aging - 10-15% per decade
 - All studies but one show this
- Manages circadian rhythm of inner clock
 - Lowers body temperature
 - Controls sleep wake cycle

Melatonin

- Free Radical Scavenger
- Decreases pro-inflammatory cytokines
- Decreases damage from beta amyloid

- Rosales-Corral S et al. Orally administered melatonin reduces oxidative stress and proinflammatory cytokines induced by amyloid-beta peptide in rat brain: a comparative, in vivo study versus vitamin C and E.
J Pineal Res. 2003 Sep;35(2):80-4.

Melatonin and NF-kappaB

- Reduces inflammatory injury through decrease in NFkB, ICAM, TNF alpha
- Li JH et al. Melatonin reduces inflammatory injury through inhibiting NF-kappaB activation in rats with colitis. *Mediators Inflamm.* 2005 Aug 31;2005(4):

Melatonin, pain, sleep

- Mu receptor agonist
- GABA receptor agonist
- Sedative and analgesic effects
- Anti-oxidant and free radical scavenger
- Capable of providing a pain free sleep so that the body may recuperate and restore itself to function again at its peak capacity

- Ebadi M et al. Pineal opioid receptors and analgesic action of melatonin. *J Pineal Res.* 1998 May;24(4):193-200.
- Golombek DA et al. Chronopharmacology of melatonin: inhibition by benzodiazepine antagonism *Chronobiol Int.* 1992 Apr;9(2):124-31.