Hormones and Pain

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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.

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

PGE2 and brain

- PGE2 in medulla needed for neuropathic pain

PGE2 and RA

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

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
Thoracic surgical wounds increase pain-related behavior and CSF and tissue PGE2 levels, all of which can be attenuated by oral cyclooxygenase inhibitors.

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

Vitamin D
CRP
Adhesion molecules VCAM1, ICAM1, MCP1, MadCAM1
Anti-oxidants Glutathione
EPA
DHA from Fish OIL
Resveratrol
EPC’s

Angiotensin II

EPA, DHA

Chronic Illness
ASCVD
TXA2
Atherosclerosis

PGE2: Pain Cancer Skin aging

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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

THE OMEGA-6 PATHWAY

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

Delta-6 Desaturase (D6D)

Gamma-linolenic acid (GLA) 18:3n-6
(Evening primrose, borage, black currant oils)

Elongase enzyme

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

Delta-5 desaturase (D5D)

THE OMEGA-3 PATHWAY

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

Delta-6 Desaturase (D6D)

Octadecatetraenoic acid 18:4n-3

Elongase enzyme

Eicosatetraenoic acid 20:4n-3

Delta-5 desaturase (D5D)

LA and LNA compete for D6D

High carb diets which cause increased insulin levels increase AA

Insulin Activates D5D

Glucagon EPA inhibits D5D

Good Eicosinoids

D6D decreased
Age > 30
< 6 months
viral infections

Trans fats
Short n-3
Long n-3
Cortisol

Slow cooked oatmeal
Breast milk

Sunflower, peanut
Leukotrienes LB4, LC4

Series 4
Very Bad Eicosinoids

PGA2

Very Bad Eicosinoids

PGA1

Delta-5 desaturase (D5D)

Delta-4 desaturase (D4D)

Arachidonic acid (AA) 20:4n-6
(Butter, lard, animal fats, brain, organ meats, egg yolk)

Eicosapentaenoic acid (EPA) 20:5n-3
Fish Oil

Docosapentaenoic acid 22:5n-3

Docosahexaenoic acid (DHA) 22:6n-3
Fish Oil
Breast Milk

Elongase enzyme

Anti-tumor
Anti-Inflamm

Series 3
Prostaglandins
PGE₃ PGH₃ PGI₃ TXA₃ & leukotrienes

Very Good Eicosinoids

Needed for Development & Function of Brain
Prostaglandins, Thromboxanes, Leucotrienes, Lipoxins, Hydroxylated Fatty acids

Vasoconstriction, Atherosclerosis, Plaque formation

Prostacyclin, Vasodilation,

Viral replication

Breast Cancer

COX, LOX are key enzymes for eicosanoid synthesis

COX, LTB4, PGE2, Lipoxins, Hydroxylated Fatty acids

PGI2, PGA2 cytoprotective

Blocked by COX2 inhibition

Not all “bad” Eicosanoids are bad

Pain, Vasoconstriction, Atherosclerosis, Plaque formation
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-κB

- Nuclear Factor Kappa Beta is central to inflammation, pain, atherosclerosis, cancer, cognitive function and more
- PGE2 can be controlled by NFκB control
- Cytokine amplification pathway
  - IL6, IL1β, TNF alpha

Positive regulatory loop

- Inflammatory signals
  - Proinflammatory cytokines
  - Protein kinase C activation
  - Viruses
  - Oxidants

- Cell membrane
- Cytoplasm
- Nucleus

- Inflammatory proteins
  - Receptors
  - Chemokines
  - Adhesion molecules
  - Enzymes
  - Cytokines

- COX
- LOX
- VCAM
- ICAM

Amplifying loop
- p50
- p65
- NF-κB
- TNF-α, Interleukin-1β
- mRNA

Inflammatory gene
**Unified Theory of Wellness:**

**Chronic Inflammation Is the Cause and the Effect of the Diseases of Aging**
Cytokines and cancer pain

- Cancer symptoms including pain, fatigue, sleep disturbance, cognitive dysfunction and affective symptoms are secondary to NFKB expression

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

Omega 3 and RA

- Placebo controlled, double blind
- 130 mg/kg/day of omega 3 fatty acids or 9 capsules/day of corn oil.
  
  \[130 \text{mg} \times 70\text{kg} = 9.1 \text{ g of omega 3 fatty acids}\]
- 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

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.

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 QoL
  - 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

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

Opioid endocrinopathy

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

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

Intrathecal opioids and hormones

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

Testosterone and pain

- Testosterone increases pain threshold
- Decreases inflammatory cytokines
- Opioid treatment decreases 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.
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

Hypothalamus

GnRH

Anterior Pituitary

FSH

LH

Testes

Leydig cell

Sertoli cell

Sperm

Estrogens

Aromatase

DHT

5-alpha Reductase

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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.

TRT improves angina pain

- Improves causes of angina
- Raises pain threshold?

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.

TRT increases pain threshold

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


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


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.
Hormones and RA

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

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 ($P = 0.0005$).

T and ankylosing spondylitis

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

T and osteoarthritis

- Positive association with serum testosterone at all tibial cartilage sites

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 QoL
- 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

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.

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.

IGF-1 in FM vs. Control

Bennett RM et al.
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

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

Somatostatin

GHRH

GHRP

GHRELIN

GH

IGF-1

LIVER

STOMACH

Hypothalamus

Anterior Pituitary

Somatostatin

THYMUS

BRAIN

GONAD

FAT

Muscle, Bone, Cartilage
GH and Crohn’s Disease

- Significant improvement in patients treated with GH
- Side effects minor and transitory

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

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
Melatonin - N-acetyl-5-methoxytryptamiine

- 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

Melatonin and NF-kappaB

- Reduces inflammatory injury through decrease in NFKB, ICAM, TNF alpha

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