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## **The Cytokine Connection to Insomnia**

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## The Cytokine Connection to Insomnia

Dr Mary Bove

## What is a Cytokine

- Regulatory glycoproteins that act as intercellular chemical messengers of the immune system
- Regulate lymphocyte function
- Regulate natural immunity
- Activation of inflammatory cells
- Stimulate hematopoiesis

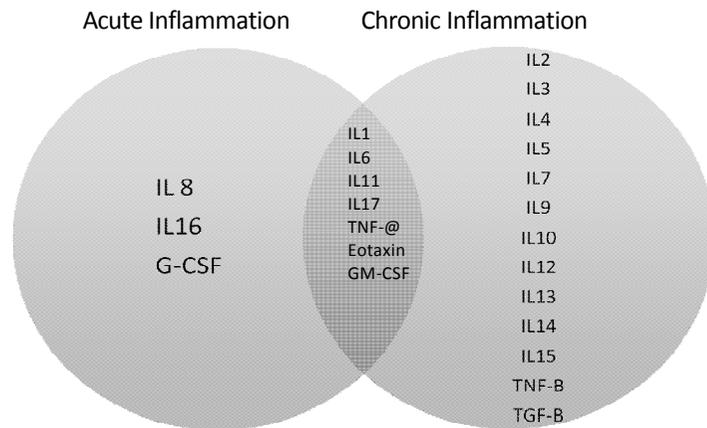
## What is a Cytokine

- Cytokines are proteins acting as neuro-immune modulators, some which help promote sleep and some that can promote sleep disruption.
- Specific cytokines are stimulated by chronic infection and inflammation or with persistent stress may lead to sleep disruption and insomnia.
- Long-term lack of sleep increases the risk of obesity, diabetes, and cardiovascular disease, chronic diseases all linked to cytokine imbalance.

## What is a Cytokine

- Interleukin 1 (IL 1), IL 6, and tumor necrosis factor (TNF) are typical examples of multifunctional cytokines involved in the regulation of the immune response, hematopoiesis, and inflammation.

## Cytokines of Inflammation



## Role of Cytokines in Sleep Regulation

- Both IL1 and TNF have been linked to a variety of clinical conditions involving sleep disorders.
- TNF is elevated in patients with chronic fatigue syndrome, chronic insomniac patients, postdialysis fatigue, preeclampsia, alcoholism, myocardial infarction, influenza virus infections, rheumatoid arthritis, and sleep apnea.

Curr Pharm Des. 2008; 14(32): 3408–3416.

## Role of Cytokines NREMS

- IL-1 plays a role with non rapid eye movement sleep (NREMS)
- NonREM sleep is promoted by a slight increase in cytokine levels, but suppressed by prominent increases.
- Conditions that enhance endogenous production of IL1 or TNF such as excessive food intake or infectious disease promote NREMS

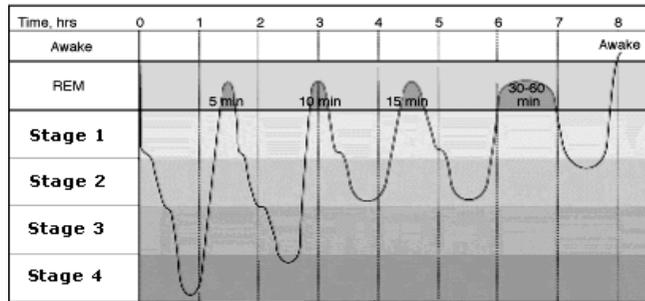
Curr Pharm Des. 2008; 14(32): 3408–3416.

## NREM and REM Pattern

- Sleep consists of non-rapid eye movement (NREM) and rapid eye movement (REM).
  - NREM: high voltage, slow delta waves on EEG
    - Sleep begins with NREM
    - NREM constitutes 75-80% of sleep
  - REM: rapid eye movements, low voltage mixed EEG, muscle atonia
    - Interrupts NREM at about 90 minute intervals
    - Waking from REM produces the most vivid dream recall

A. Rechtschaffen. Perspectives in Biology and Medicine. 1998;41(3):359.

## NREM and REM Pattern

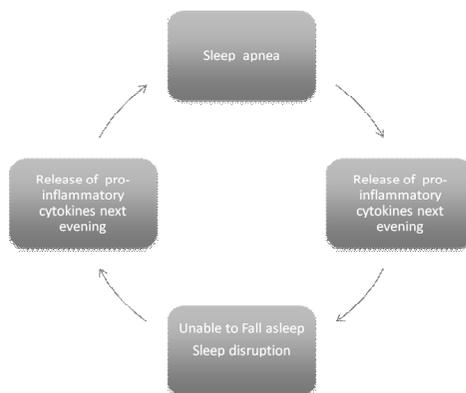


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## Cytokine Communication

- Bi-directional communication pathways exist between the brain and the cytokine-immune-endocrine systems.
- Changes in cytokine levels in the periphery modulate the central nervous system either directly or via the vagal nerve and influences the sleeping/waking brain.

## Cytokine Sleep Vicious Cycle



## Chronic Pain and Inflammation

- Pro-inflammatory cytokines IL-6 and TNF $\alpha$  daytime secretion is elevated in insomniacs
- Controlling chronic pain and inflammation may improve sleep, daytime alertness, and performance

Sleep Med Clin. 2007 June; 2(2): 279-291.

## Stress and Cytokines

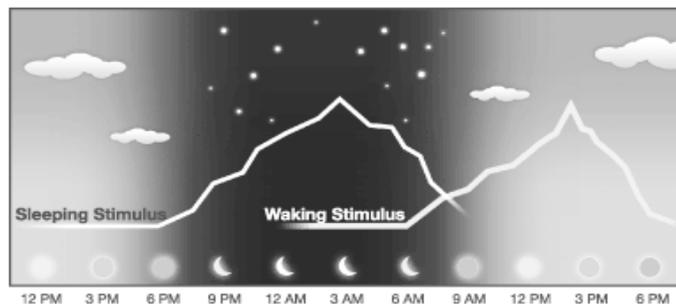
- Stress promote inflammatory responses through effects on sympathetic and parasympathetic nervous system pathways
- Proinflammatory cytokines have been found to interact with neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and behavior.

## Circadian Sleep/Wake Brain

- In humans, circadian nocturnal sleep-daytime wakefulness is associated with changes in peripheral cytokines, cellular immune functions, and endocrine influences.
- The interaction between the circadian sleeping/waking brain and the cytokine-immune-endocrine system are integral to preserving homeostasis.

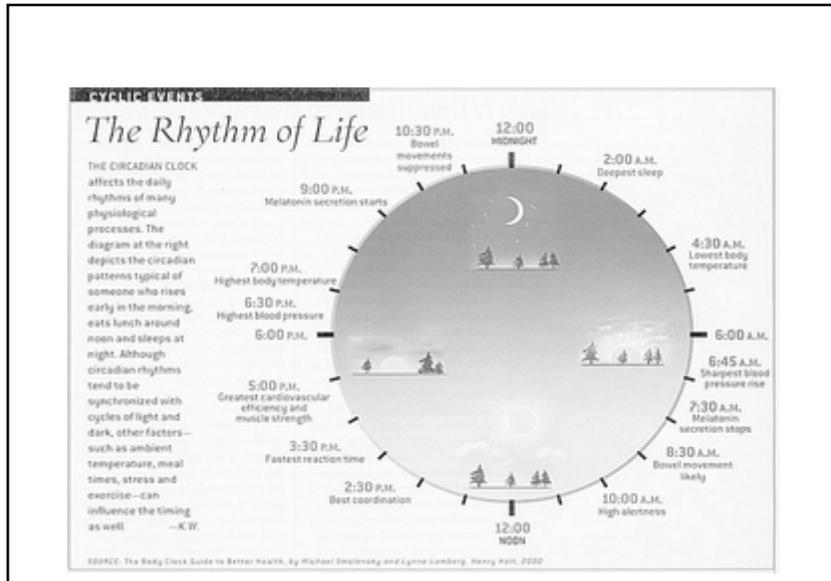
[http://dx.doi.org/10.1016/S1087-0792\(99\)90003-5](http://dx.doi.org/10.1016/S1087-0792(99)90003-5)

## Circadian Rhythm



## Circadian Rhythm Sleep Disorders

- Sleep disorders affecting the timing of sleep.
- People with circadian rhythm sleep disorders are unable to sleep and wake at the times required for normal work, school, and social needs.
- Generally able to get enough sleep if allowed to sleep and wake at the times dictated by their body clocks.
- Unless they also have another sleep disorder, their sleep is of normal quality.



## What can drive Cytokines?

- Dietary, Nutritional
- Allergy or Sensitivity
- GI Issues mucosal health (integrity, IgA, Peyer's patches)
- Dysbiosis - GI, GU, Respiratory, Integument, Renal
- Exogenous Toxins
  - Heavy metals
  - Chemical
  - Medication
- Stress/Mind/Body Coping with illness, past/present traumas
- Chronic infection
- Trauma, Chronic pain
- Hormonal
  - Adrenal, thyroid, Sex hormones

## Botanical Therapeutic Approach

- A multi-focused approach
  - Modulating cytokines
  - Modulating neurotransmitters
  - Quenching inflammation
  - Re-regulating the immune system
  - Eliminating any potential triggers
  - Improve HPA axis function- adaptogens
  - Use nervines and sedatives as needed

## Herbal Combinations in Therapeutic Protocols for Sleep Disruption

- Anti-inflammatory acting herbs
- Immunomodulators
- Adaptogens
- Nervines and Relaxants
- Sedatives and Soporifics
- Analgesic

## Cytokine Modulators

- Herbal medicines, known as immunomodulators, alters the activity of immune function through the dynamic regulation of informational molecules such as cytokines
  - Allium sativum
  - Echinacea purpurea
  - Panax ginseng
  - Silybum marianum
  - Uncaria tomentosa
  - Withania somnifera

Alternative Medicine Review • Volume 11, Number 2 pp 128-150 • 2006

## Anti-Inflammatory Acting Plants

- Turmeric/*Curcuma longa*
- Black pepper/*Piper nigrum*
- Devil's Claw/*Harpogophytum Procumbens*
- Green Tea/ *Camellia*
- Holy Basil/*Ocimum sanctum*
- Resveratrol

## Adaptogen with Cytokine Lowering Action

- Ashwaganda/*Withania somnifera*
- Astragalus root/***Astragalus membranaceus***
- Holy Basil/*Ocimum sanctum*
- Maitaki mushroom/*Grifola frondosa*

## Anagelics, Nevinces & Sedative Plants with Cytokine Lowering Action

- Fresh Milky Oats/*Avena sativa*
- Jamacian Dogwood/*Piscidia erythrina*

Combine with one or more other plants with soporific actions such as Passionflower, Hops, or Lemon Balm

## **Black pepper** Piper nigrum

- Group of alkaloids called piperamides, giving the spicy pungent flavor. The main one being known as piperine.
- Protects against oxidative damage by inhibiting free radicals and reactive oxygen species
- lower lipid peroxidation
- enhance the bioavailability of a number of therapeutic drugs as well as phytochemicals

Crit Rev Food Sci Nutr. 2007;47(8):735-48.

## **Piperine and Drug Metabolism**



- The alkaloid piperine acts to enhance the oral absorption of concomitantly administered medications.
- Piperine's action on inhibiting drug metabolism was first recognized more than 30 years ago.
  
- 5 mg piperine = 2 fold increase in curcumin AUC.
- 20 mg piperine = ~ 20 fold increase in curcumin AUC.

Anand P, et al. Mol Pharmacol 2007; 4: 807-818

## **Black pepper** Piper nigrum

- Piperine's bioavailability enhancing property is also partly attributed to increased absorption as a result of its effect on the ultrastructure of the intestinal brush border



## **Turmeric** Curcuma longa

- Curcuma is a functional food
- AC - turmerin, essential oils, and curcuminoids. Curcuminoids are polyphenolic compounds. Curcumin main therapeutic polyphenol
- Exhibits antioxidant, anti-inflammatory and anti-cancer properties
- Crosses the blood-brain barrier
- Neuroprotective in neurological disorders

Current Pharmaceutical Design, Volume 18, Number 1, January 2012, pp. 91-99(9)

## Curcumin

- Immunomodulatory agent that modulates the activation of T cells, B cells, macrophages, neutrophils, natural killer cells, and dendritic cells.
- Curcumin downregulates the expression of various proinflammatory cytokines including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines likely through inactivation of the transcription factor NF- $\kappa$ B.

<http://lpi.oregonstate.edu/infocenter/phytochemicals/curcumin/>

## Curcumin

- Curcumin has been found to inhibit COX-2 activities mainly by inhibiting its transcription
- Nuclear factor-kappa B (NF- $\kappa$ B) is a transcription factor that binds DNA and enhances the transcription of the COX-2 gene as well as other pro-inflammatory genes, such as inducible nitric oxide synthase (iNOS).
- In inflammatory cells, such as macrophages, iNOS catalyzes the synthesis of nitric oxide, which can react with superoxide to form peroxynitrite, a reactive nitrogen species that can damage proteins and DNA.
- Curcumin has been found to inhibit NF- $\kappa$ B-dependent gene transcription, and the induction of COX-2 and iNOS

<http://lpi.oregonstate.edu/infocenter/phytochemicals/curcumin/>

## Curcumin

- Glutamate cysteine ligase (GCL), the rate-limiting enzyme in glutathione synthesis.
- Studies in cell culture suggest that curcumin can increase cellular glutathione levels by enhancing the transcription of genes that encode GCL

Free Radic Biol Med. 2007;43(3):444-453

## Curcumin

- It is unclear whether doses less than 3.6 g/day are biologically active in humans
- Limited oral bioavailability in humans
- Curcumin supplementation (1,200 mg/day)
- Piperine for increasing the bioavailability of curcumin

## Dosing and Bioavailability

- A clinical trial conducted in the UK found that plasma concentrations of curcumin, curcumin sulfate, and curcumin glucuronide were in the range of 10 nanomoles/liter (0.01 micromole/liter) one hour after a 3.6 g oral dose of curcumin
- Curcumin and its metabolites could not be detected in plasma at doses lower than 3.6 g/day.
- Curcumin and its glucuronidated and sulfated metabolites were also measured in urine after a dose of 3.6 g/day.

Clin Cancer Res. 2004;10(20):6847-6854

## Piperine and Curcumin

- Piperine appears to have a positive effect on apical-to-basal permeability and uptake of Curcumin
- Combination improves the bioavailability of Curcumin

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## Herbal Combinations

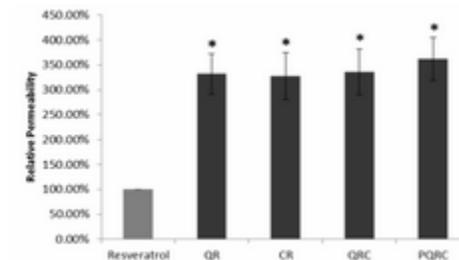
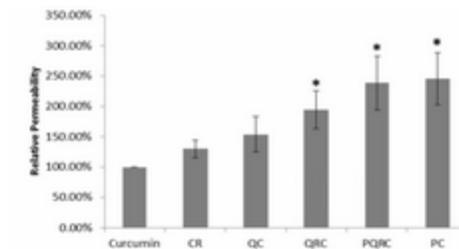
(quercetin, resveratrol, curcumin and piperine)

- quercetin, resveratrol, curcumin
- Data suggests that delivering these compounds in combination may improve the acute bioavailability and significantly increase apical-to-basal uptake of curcumin and resveratrol compared to supplementation with single compounds.

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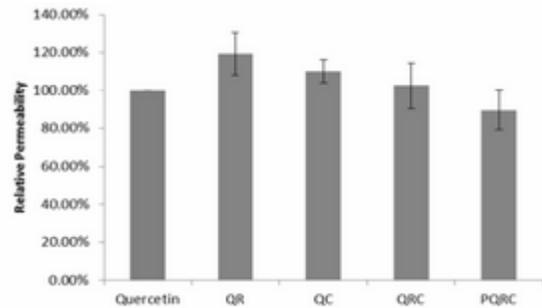
The addition of Piperine appears to have a positive effect on apical-to-basal permeability, especially in the case of curcumin, less so on resveratrol.

C=Curcumin  
Q=Quercetin  
R=Resveratrol  
P=Piperine



Lund, Pantuso, 2013

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- Quercetin had no significant change in bioavailability when combined with the other compounds.

Lund, Pantuso, 2013

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## Devil's Claw *Harpagophytum procumbens*

- Iridoid glycosides, components believed to have strong anti-inflammatory effects. harpagogide, procumbide, and harpagoside
- Dosage;
  - 250-435mg three times a day to alleviate pain
  - 1,800-2,400 mg (50-100 mg harpagoside) daily for arthritis and musculoskeletal pain and inflammation
- All extracts are not equally effective; whole-plant extracts appear to have a better therapeutic effect than those prepared from isolated parts.

Alternative Medicine Review Volume 13, Number 3 2008

## Devil's Claw *Harpagophytum procumbens*

- An ethanolic extract of Devil's Claw in activated monocytes was able to dose-dependently reduce the release of proinflammatory cytokines TNF- $\alpha$ , IL-6, PGE<sub>2</sub>, and IL-1 $\beta$  with significance at 100mcg/mL or above & nearly abolishing TNF- $\alpha$  release at 500mcg/mL

Fiebich BL, et al. *Phytother Res.* 2012

- Inhibition of inflammatory mediators, including COX-2, leukotrienes, nitric oxide, TNF- $\alpha$ , and interleukin-1  $\beta$

Alternative Medicine Review Volume 13, Number 3 2008

## Green tea *Camellia sinensis*

- Studies have shown that in large groups of people that consumed eight to twelve cups of green tea daily have lower amounts of pro-inflammatory cytokines

Nutrition. 2011 February; 27(2): 206–213.

## Lowering IL-6

- Epigallocatechin-3-gallate (EGCG), luteolin, & apigenin inhibit IL-6 production
- 2 cups Green Tea daily
- Good dietary sources of luteolin and apigenin include: onions, broccoli, celery hearts, hot peppers, artichokes, rutabagas, spinach, fennel, parsley, chives, peppermint, thyme

## Green Tea *Camellia sinensis*

- One 275 -300 mg capsule standardized to >80% polyphenols and >50% EGCG) is equal to two cups of green tea
- Each capsule contains less than 3 mg caffeine.
- Prevention dosing: 2 – 4 capsules
- Therapeutic dosing: 4 – 6 capsules
- Take with food

## Holy Basil *Ocimum sanctum*

### **Actions:**

Adaptogen, analgesic, anodyne, antiviral, antibacterial, antifungal, anti-allergic, galactagogue, radioprotective, hypoglycemic, hypocholesterolaemic, COX-II anti-inflammatory agent, cortisol regulator, tonic, immunomodulating,

### **Active Constituents:**

Alkaloids, oleanolic acid, ursolic acid, tannins rosmarinic acid, eugenol, carvacrol, linalol,  $\beta$ -caryophyllene, saponins, flavonoids,

## Holy Basil

- Aids in lowering fasting and post-meal blood sugars
- Cortisol reducing compounds
- Ursolic acid, a constituent in Holy Basil, reveals its activity as an anti-inflammatory and COX-2 inhibitor
- Enhances the activity of glutathione S-transferase, a key enzyme in detoxification

## Holy Basil *Ocimum sanctum*



### Preparations:

- Dried powder-250-1000mg/d
- Fresh leaf as tea or food
- Herbal tea 1-3 cups daily
- Tincture; 4-10mls daily
- Mixed powdered herb with ghee

## Jamacian Dogwood *Piscidia erythrina*



- Phytochemistry - isoflavones, glycosic tannins, resins, organic acids, volatile and  $\beta$ -sitosterol
- Actions-Analgesic, Anti-inflammatory, Antispasmodic, Nervine, Sedative
- *Piscidia erythrina* produced a pharmacological effect between the sedative action of *Valeriana* and the anti-anxiety activity of *Passiflora*

Riv-Neurol 1981 ; 51 : 297-310

## Jamacian Dogwood *Piscidia erythrina*



- Dosing; use 1-3 times daily
  - Decoction of the dry roots 1-2 grams
  - Tincture -1:5, use 3-5 ml/dose
  - Fluid Extract -1:1 use 1-2ml/dose
  - Solid Extract -500 mg/ dose

## Oats *Avena sativa*

- Alkaloid – Gramine
- Organic acids, Flavonoids, Triterpene Saponin
- Inhibits the secretion of proinflammatory cytokines IL-6 chemokines IL-8
- Traditional uses nervous irritation, depression, sleeplessness, nervous exhaustion, nervous weakness

## Herbal Combinations for Modulating Cytokine and Sleep Patterns

- Morning to Mid-day
  - Adaptogens
  - Immunomodulators
- Mid-day to Evening
  - Adaptogens
  - Immunomodulators
  - Anti-inflammatory
- Evening to Bed
  - Anti-inflammatory
  - Nervine, Sedative, Analgesic

## Herbal Combinations for Modulating Cytokine and Sleep Patterns

- Morning to Mid-day
  - Holy Basil/Ashwaganda
  - Echinacea/ Milk Thistle
- Mid-day to Evening
  - Holy Basil/Ashwaganda
  - Echinacea/ Milk Thistle
  - Tumeric/Curcumin w/ piperine & Resveratrol -150mg
- Evening to Bed
  - Tumeric/Curcumin w/ piperine & Resveratrol-150mg
  - Jamacian Dogwood/Avena – evening & bedtime dose