EPIGENETICS AND CHRONIC PAIN

Robert Melashenko MD
Disclaimer

• NONE
Drugs:

Opiates

NSAIDS
Neurology

Chronic Pain Fuels Boom in Opioids

Published: Feb 19, 2012

By John Fauber, Reporter, Milwaukee Journal Sentinel/MedPage Today
These national organizations used positions, statements, guidelines, books and doctor education courses to pave the way for the growing use of opioids in treating chronic pain.

<table>
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<th>The money</th>
<th>The message</th>
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<td>From 1999 through 2010, got $2.5 million from opioid companies.</td>
<td>Through positions and papers helped liberalize how opioids are prescribed and viewed.</td>
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<td>In recent years got millions of dollars from industry, including opioid companies.</td>
<td>Issued an opioid friendly patient guide in 2006.</td>
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<td>Last year got nearly $1.5 million from the pharmaceutical industry.</td>
<td>Co-issued a 1996 consensus statement endorsing opioids for chronic pain.</td>
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<td>In the last two years, got $1.6 million from opioid companies.</td>
<td>Issued model guidelines/policy on the use of opioids in 1998, updated in 2004.</td>
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<td>Federation's foundation got an undisclosed amount from opioid companies for a book on opioid prescribing.</td>
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Federation maintained: “[Our] most recent policy reflects the considerable body of research and experience accrued since our last series of formal policies related to opioid prescribing and addiction were adopted in 2004. Our latest guidelines, adopted this year, acknowledge that evidence for the risk associated with opioids has surged, while evidence for the benefits of opioids for long-term use has remained controversial and insufficient.”
By 2010, the United States, with about five per cent of the world’s population, was consuming ninety-nine per cent of the world’s hydrocodone (the narcotic in Vicodin), along with eighty per cent of the oxycodone (in Percocet and OxyContin), and sixty-five per cent of the hydromorphone (in Dilaudid).
A Flood of Opioids, a Rising Tide of Deaths

Susan Okie, M.D.

Death Rate per 100,000


Deaths from Unintentional Drug Overdoses in the United States According to Major Type of Drug, 1999–2007

U.S. Rates of Death from Unintentional Drug Overdoses and Numbers of Deaths, According to Major Type of Drug.

Shown are nationwide rates of death from unintentional drug overdoses from 1970 through 2007 (Panel A) and the numbers of such deaths from opioid analgesics, cocaine, and heroin from 1999 through 2007 (Panel B). Data are from the National Vital Statistics System, Centers for Disease Control and Prevention.
Nonsteroidal drugs (inhibitors of cyclooxygenases I and II) will provide symptomatic relief of pain but these drugs, on balance, have very limited effects on inflammation. That is, they poorly suppress the inflammatory response.
Review

Is COX-2 a perpetrator or a protector? Selective COX-2 inhibitors remain controversial

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Inducible cyclooxygenase may have anti-inflammatory properties

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In the treatment of rheumatoid arthritis, NSAIDs are administered for several months or even years and yet they show little evidence of decreasing disease progression or joint destruction\textsuperscript{17}. Perhaps these results may help to explain the lack of long-term disease-modifying activity and the persistence of rheumatoid arthritis in patients receiving NSAID therapy. Other work in the

In summary, our results indicate that during the PMN-dominated, early phase of a carrageenin-induced pleurisy, COX 2 may be pro-inflammatory. However, during the later, MN cell-dominated phase, COX 2 may regulate resolution of acute inflammation by generating an alternate set of prostaglandins such as those of the cyclopentenone family.
Fig. 1. The metabolism of n-3 and n-6 PUFA and the biosynthesis of their respective eicosanoid and proresolving mediators. n-3 PUFAs are generally less inflammatory than the n-6 PUFA. However, PGE_2 derived from n-6 PUFA can have an anti-inflammatory effect by decreasing LTB_4 production by the inhibition of 5-LOX and increasing production of LXA_4 by stimulating 15-LOX. n-3 PUFA-derived eicosanoids have different physiological potencies than n-6 PUFA-derived eicosanoids. Abbreviations: HPETE, hydroperoxyeicosatetraenoic acid; LT_A_4, leukotriene A_4; LX_A_4 lipoxin A_4.
Aspirin: Antiinflammatory Drug of Choice in 2011?

In 1974, the US Food and Drug Administration (FDA) approved another new NSAID, ibuprofen. Although initial trials in patients with rheumatoid arthritis showed no benefit over placebo, ibuprofen, through successful promotion, soon became one of the most popular non-ASA NSAID3.

Non-ASA NSAID have been found to increase blood pressure in hypertensive and even in normotensive people. This hypertensive effect is dose-dependent and involves, at least in part, the inhibition of cyclooxygenase-2 (COX-2) in hemodialysis. Acetaminophen and non-ASA NSAID use were both found to be associated with increased risk of end-stage renal disease (ESRD) in a dose-dependent manner. Again, ASA was found not to have an increased odds ratio of ESRD13.
“Doctors end up chasing pain” instead of focusing on treating the underlying condition, she said. (Claire Trescott MD)

But what is the “underlying” condition?
can themselves cause tissue damage. In 1972, Lewis Thomas said “Our arsenals for fighting off bacteria are so powerful, and involve so many different defense mechanisms, that we are more in danger from them than the invaders. We live in the midst of explosive devices; we are mined.” (Germs, *N Engl J Med*, 1972, 287:553–555.)
Neuroinflammation and the generation of neuropathic pain

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Editor’s key points

- There is increasing evidence of the role of inflammatory processes in neuropathic pain.
- Peripheral inflammatory mediators can sensitize the nervous system, both peripherally, and centrally.

Targeting excessive inflammation as a therapy for neuropathic pain
Figure 17.4. Firing of small afferents in the skin (left) occurs with increasing frequency with increasing temperatures. Following carrageenan injection into skin, afferent shows increasing spontaneous activity, a left shift, and an increase in slope of stimulus-response curve, indicating a facilitated response to the thermal stimulus (Right). Firing of articular afferent under normal state and in presence of non-noxious and then noxious rotation of knee. After injection of irritant into joint, mild rotation results in significant discharge.
The major discovery of Serhan’s work is that the conclusion of an inflammation is a controlled process of the immune system (IS) and not simply the consequence of an extinguished or “exhausted” immune reaction.
Figure 2

Chemical mediators: Prostaglandins, Leukotrienes

"unresolved"

Acute Inflammation

Chronic Inflammation

Fibrosis

Lipid mediator class switching

PGE₂, PGD₂, LTB₄

LX

Resolution

Programmed Resolution

Return to homeostasis

Families Specialized Pro-Resolving Mediators (SPM)

SPM

Lipoxins

Resolvins

Protectins/Neuroprotectins

Edema

PMNs

Monocytes/Macrophages

Activity

time

1 2 3

RvE1

RvD1

PD1

A Novel Genus Endogenous Lipid Mediators


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Nonresolving Inflammation

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Inflammation is an inherent feature of inflammation. Neutrophils are the principal phagocytes responsible for clearing pathogens, but a failure to resolve inflammation can lead to chronic conditions such as atherosclerosis, chronic obstructive pulmonary disease, rheumatoid arthritis, inflammatory bowel disease, and others. The figure illustrates mechanisms and consequences of nonresolution of inflammation.
Arachidonic acid-derived epoxyeicosatrienoic acids (EETs) produced by cytochrome P450 epoxygenases represent yet another class of anti-inflammatory lipids. EETs can inhibit NF-κB and block induction of COX2 and 5'-lipoxygenase (Node et al., 1999).

COX2 has also been found to switch from producing the predominantly proinflammatory PGE2 early in inflammation to producing cyclopentanone prostaglandins later on, such as 15-deoxy-Δ^{12,14}-prostaglandin J. The latter blocks endothelium from expressing VCAM-1, macrophages from releasing chemokines, and adherent neutrophils from producing ROI, among other anti-inflammatory actions (Lawrence et al., 2002). Thus, while administration of COX2 inhibitors early is anti-inflammatory, their late administration can prolong inflammation (Gilroy et al., 1999), and there is a similar concern with 5'-lipoxygenase inhibitors (Serhan, 2007). This may help explain COX2 inhibitors to limit brain damage in stroke.

Another form of persistent stimulation of inflammation arises from the biosynthetic incorporation of a foreign food antigen into self-molecules, with which antibodies then react. For example, humans have a loss-of-function mutation in a gene encoding an enzyme required for production of N-glycolylneuraminic acid (Neu5Gc), which the human immune system can therefore recognize as foreign (Hedlund et al., 2008). Dietary Neu5Gc is taken up from red meat and dairy products, incorporated into cell surface glycans, and bound by antibody. The resulting inflammation appears to promote angiogenesis and oncogenesis in a COX2-dependent manner (Hedlund et al., 2008).
Although there are multiple definitions of pain, most experts agree that it is primarily a sensory experience. There are two major components that contribute to perioperative pain, namely inflammatory and neuropathic pain. Both of these states share multiple common features and can be experienced either jointly or separately.
...observations reveal a previously unrecognized mechanism to communicate RNA-based signals between the hematopoietic system and various organs, including the brain in response to inflammation.
DNA → RNA → protein
Eating ourselves to death (and despair): The contribution of adiposity and inflammation to depression

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Diet & Inflammation

Sialic Acid

PUFA’s

Intestinal Microbiota
A difference in one molecule led physician Ajit Varki to question what sets humans apart from other apes. Bruce Lieberman meets a man who sees a big picture in the finer points.
SMALL CHANGE, BIG DIFFERENCE

A mutation during human evolution means that humans accumulate the sialic acid Neu5Ac whereas other primates also make Neu5Gc.

On a molecular level, the difference between Neu5Gc and Neu5Ac is tiny — a single added oxygen atom perched on one arm distinguishes one from the other (see graphic). But on a biological level, the difference could be enormous.

Chimpanzees don’t get sick from the human malaria parasite, *Plasmodium falciparum*. Conversely, humans can’t be infected with *P. reichenowi*, the malaria parasite that plagues chimpanzees.

In subsequent work, Varki and his team showed that the different susceptibilities were due to the differences in sialic acids. *P. reiche-
Human uptake and incorporation of an immunogenic nonhuman dietary sialic acid

Pam Tangvoranuntakul*, Pascal Gagneux*, Sandra Diaz*, Muriel Bardor*, Nissi Varki*, Ajit Varki* †, and Elaine Muchmore‡

*Glycobiology Research and Training Center, Departments of Medicine and Cellular and Molecular Medicine, University of California at San Diego, La Jolla, CA 92093-0687; and †San Diego Veterans Affairs Medical Center, La Jolla, CA 92161

Edited by Sen-itiroh Hakomori, Pacific Northwest Research Institute, Seattle, WA, and approved August 18, 2003 (received for review March 18, 2003)

Neu5Gc has never been reported in plants or microbes to our knowledge. We found that Neu5Gc is rare in poultry and fish, common in milk products, and enriched in red meats. Furthermore, normal humans have variable amounts of circulating IgA, IgM, and IgG antibodies against Neu5Gc, with the highest levels comparable to those of the previously known anti-α-galactose xenoreactive antibodies. This finding represents an instance wherein humans absorb and metabolically incorporate a nonhuman dietary component enriched in foods of mammalian origin, even while generating xenoreactive, and potentially autoreactive, antibodies against the same molecule. Potential implications for human diseases are briefly discussed.
Fig. 5. ELISA detection of anti-Neu5Gc antibodies in normal human sera and demonstration of specificity. (A) Results are plotted as mean background values with PAA-Neu5Ac subtracted from the signal with PAA-Neu5Gc. The mean value for all positive sera in each subclass is represented by the horizontal bar. (B) Two of the human sera identified as medium or high positive for anti-Neu5Gc IgG antibodies to the target Neu5Gc-PAA were tested in the same ELISA with dilutions of chimpanzee serum added to inhibit binding. A human serum with undetectable anti-Neu5Gc antibodies was used as a control.
Evidence for a novel human-specific xeno-auto-antibody response against vascular endothelium

A

Chicken Anti-Neu5Gc IgY

Endothelium

Lumen

Chicken Anti-Neu5Gc IgY

Control IgY

Placenta

Colon

x200

by immunohistochemistry with both a monospecific chicken anti-Neu5Gc antibody and with affinity-purified human anti-Neu5Gc antibodies demonstrates endothelial expression of Neu5Gc, likely originating from Neu5Gc-rich foods like...
Probiota
The numbers are staggering.

<table>
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<th>Human</th>
<th>Microbes</th>
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<td>10 Trillion Cells</td>
<td>100 Trillion Cells</td>
</tr>
<tr>
<td>~ 21,000 P.C genes</td>
<td>2-3 Million P.C. genes</td>
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By these measures, we are 99% bacterial.

At the “Body Board Meeting” who sets policy?
Fig. 1. The bi-directional microbiota–gut–brain axis. Changes in the microbiota alter gut and brain function. Behavioural perturbation alters gut function, changes the habitat for bacteria and alters the composition of intestinal commensal bacteria.
Microbiota, the immune system, black moods and the brain—melancholia updated

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³ Department of Psychology, Center for Brain and Cognition, University of California, San Diego, San Diego, CA, USA

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Polyunsaturated Fatty Acids

( PUFA’s )
Fig. 1. The metabolism of n-3 and n-6 PUFA and the biosynthesis of their respective eicosanoid and proresolving mediators. n-3 PUFAs are generally less inflammatory than the n-6 PUFA. However, PGE2 derived from n-6 PUFA can have an anti-inflammatory effect by decreasing LTB4 production by the inhibition of 5-LOX and increasing production of LXA4 by stimulating 15-LOX. n-3 PUFA-derived eicosanoids have different physiological potencies than n-6 PUFA-derived eicosanoids. Abbreviations: HPETE, hydroperoxyeicosatetraenoic acid; LTA4, leukotriene A4; LXA4, lipoxin A4.
A low omega-6 polyunsaturated fatty acid (n-6 PUFA) diet increases omega-3 (n-3) long chain PUFA status in plasma phospholipids in humans

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SPINAL INJECTION OF DOCOSAHEXAENOIC ACID ATTENUATES CARRAGEENAN-INDUCED INFLAMMATORY PAIN THROUGH INHIBITION OF MICROGLIA-MEDIATED NEUROINFLAMMATION IN THE SPINAL CORD

Y. LU, a,b L.-X. ZHAO, a, D.-L. CAO a AND Y.-J. GAO a

Key words: inflammatory pain, carrageenan, docosahexaenoic acid, microglia, cytokines, chemokines.

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Diet & Healing
Vegan diet alleviates fibromyalgia symptoms

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SPECIAL TOPIC SERIES

(DClin J Pain 2004;20:19–26)

Dietary Constituents as Novel Therapies for Pain

Jill M. Tall, PhD, and Srinivasa N. Raja, MD
MicroRNA expression altered by diet: Can food be medicinal?

Joshua D. Palmer, Benjamin P. Soule, Brittany A. Simone, Nicholas G. Zaorsky, Lianjin Jin, Nicole L. Simone

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Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA, United States
Review

Epigenetic impact of dietary polyphenols in cancer chemoprevention: Lifelong remodeling of our epigenomes

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Review

Pharma–nutrition interface: The gap is narrowing

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The Effects of Diet on Inflammation
Emphasis on the Metabolic Syndrome

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Reducing the incidence of coronary heart disease with diet is possible. The main dietary strategies include adequate omega-3 fatty acids intake, reduction of saturated and trans-fats, and consumption of a diet high in fruits, vegetables, nuts, and whole grains and low in refined grains. Each of these strategies may be associated with lower generation of inflammation. This review examines the epidemiologic and clinical evidence concerning diet and inflammation. Dietary patterns high in refined starches, sugar, and saturated and trans-fatty acids, poor in natural antioxidants and fiber from fruits, vegetables, and whole grains, and poor in omega-3 fatty acids may cause an activation of the innate immune system, most likely by an excessive production of proinflammatory cytokines associated with a reduced production of anti-inflammatory cytokines. The whole diet approach seems particularly promising to reduce the inflammation associated with the metabolic syndrome. The choice of healthy sources of carbohydrate, fat, and protein, associated with regular physical activity and avoidance of smoking, is critical to fighting the war against chronic disease. Western dietary patterns warm up inflammation, while prudent dietary patterns cool it down. (J Am Coll Cardiol 2006;48:677–85) © 2006 by the American College of Cardiology Foundation
Editorial

Food and pain: Should we be more interested in what our patients eat?

A BMJ editorial comment reviewing an article on folic acid noted that doctors are generally more comfortable with drugs than with food, and that this may be due to many doctors having a limited knowledge of nutrition (Smith, 2004). Dietary interventions are attractive due to availability, low costs and low toxicity. We now know much about the toxicity of NSAIDs and coxibs, but what do we know about our pain patient’s diets?

The growing body of scientific evidence indicates that diet and nutrition may be a promising area for future pain research and pain treatment.
Fig. 10. Carcinogens activate and chemopreventive agents suppress NF-κB activation, a major mediator of inflammation.
Vegan Diet Eases Diabetic Neuropathy Pain

Published: Aug 8, 2014

Bunner noted that current treatments for diabetic neuropathy -- which occurs in about half of all type 2 diabetes patients -- only treat the pain, and do not treat the underlying cause of that pain.

An earlier observational study by Crane and Sample (J Nutr Med 1994; 4: 431-439) of 21 type 2 diabetics with nerve pain showed that being on a low-fat, high-fiber vegan diet for a month brought complete pain relief to 81% of participants, who lost about 11 pounds on average.

The majority of these patients were also able to reduce their diabetes medications and blood pressure medications.
Antioxidants in vegan diet and rheumatic disorders

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c National Research and Development Centre for Welfare and Health, Helsinki, Finland

Abstract

Plants are rich natural sources of antioxidants in addition to other nutrients. Interventions and cross sectional studies on subjects consuming uncooked vegan diet called living food (LF) have been carried out. We have clarified the efficacy of LF in rheumatoid diseases as an example of a health problem where inflammation is one of the main concerns. LF is an uncooked vegan diet and consists of berries, fruits, vegetables and roots, nuts, germinated seeds and sprouts, i.e. rich sources of carotenoids, vitamins C and E. The subjects eating LF showed highly increased levels of beta and alfa carotenes, lycopen and lutein in their sera. Also the increases of vitamin C and vitamin E (adjusted to cholesterol) were statistically significant. As the berry intake was 3-fold compared to controls the intake of polyphenolic compounds like quercetin, myricetin and kaempherol was much higher than in the omnivorous controls. The LF diet is rich in fibre, substrate of lignan production, and the urinary excretion of polyphenols like enterodiol and enterolactone as well as secoisolaricirecinol were much increased in subjects eating LF. The shift of fibromyalgic subjects to LF resulted in a decrease of their joint stiffness and pain as well as an improvement of their self-experienced health. The rheumatoid arthritis patients eating the LF diet also reported similar positive responses and the objective measures supported this finding. The improvement of rheumatoid arthritis was significantly correlated with the day-to-day fluctuation of subjective symptoms. In conclusion the rheumatoid patients subjectively benefited from the vegan diet rich in antioxidants, lactobacilli and fibre, and this was also seen in objective measures.

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Keywords: Antioxidants; Living food; Lactobacilli and fibre
THE NEW “MULTIMODAL” APPROACH IN TREATING CHRONIC PAIN

1. The goal should be an attempt to decrease and eliminate drugs instead of chasing an elusive therapeutic window.
2. All patients are counseled on decreasing inflammation via diet!
3. Narcotics reserved for acute pain “flare-ups”, not as maintenance drugs.
4. Exercise, sleep, and stress reduction given “equal billing” with drugs and procedures.
“Let food be thy medicine and medicine be thy food.”

- Hippocrates