

Stephen Barrett and Medical McCarthyism

By S.L & R.A

(Concerned that those who engage in uncontested attacks against supporters of alternative health would misconstrue me and my co-author as such, we mean to clarify the following: we are not advocates of the alternative health movement, rather, we are advocates and supporters of truth. - S.L & R.A)

Introduction

Dr. Stephen Barrett is a ubiquitous figure in the world of health and medicine with a unique talent. A talent, described by Health and Human Services official, Dr. Thomas R. Eng, as a gift for widely "[influencing] behavior change" via interactive media. Elaborating, Eng states that "[Barrett] tailors information and interactions to the individual," adding, "In print media, there is some kind of vetting. In interactive, anyone or their brother can slap a Web page together."

One assumes that Barrett, in his efforts and opinions, is authoritative and correct, speaking as a retired physician / psychiatrist who's been interviewed on innumerable occasions by CNN, The New York Times, has testified as an expert before congress, and, in a larger sense, has been adopted by mainstream media as the "consumer watchdog" du jour within the field of medicine.

Well, alternative medicine, more specifically.

He has authored reports on many of the most accomplished practitioners and experts in the alternative health movement and in doing so, has generated a fair amount of controversy and mixed media attention. So much, in fact, that the reports on his site have come to dominate web search engine results, and in effect, preemptively tainting the reputations of hundreds of legitimate, well credentialed alternative health practitioners. Upon discovering this, my curiosity was piqued and I felt compelled to conduct some independent research on the matter, and hopefully, reach a conclusion as to whether Barrett was, indeed, an expert, or guilty of what Dr. Eng describes as "medical McCarthyism".

My focus would be the history and relationship between Barrett and Dr. Gary Null. Null is arguably the most respected, prolific advocate and high-profile voice in the alternative health movement, influencing a massively wide spectrum of people throughout a varied host of

philanthropic efforts and causes. The purpose of this paper is to not to bring direct challenge to Barrett's work or ideology, but rather to present facts and convey reasoned, journalistic interrogation into the heart of this debate. To that end, we can look to Null's extensive work and research on the negative effects of fluoride, mercury, vaccines, sugar and caffeine, all of which, Barrett has called in to question. Research will demonstrate that science firmly supports all of Null's conclusions and solutions on these topics. Fact checking and research is the cornerstone of the journalistic process, yet, Barrett and those media outlets who would employ his subjective opinion as scientific fact, quite simply, have not done their homework here.

Methodology

In order to determine who is accurate Barrett or Null, I used only independent scientific, peer reviewed literature. Literally thousands of studies were examined.

Conclusions

My review finds that Dr. Barrett's claims against Null are unfounded, biased, personal attacks based on his own personal opinion. Every article of Null's that I have examined has had a preponderance of credible scientific research to support the conclusions.

Therefore, it is this journalist's opinion that Dr. Gary Null is not only accurate in the substance of his articles and documentaries on topics such as the negative health effects of fluoride, sugar, and mercury in dental fillings, but also that Barrett has engaged in unprofessional and *ad hominem* attacks on Dr. Null without scientific support. At the end of this discussion you will find samples from the peer reviewed literature from each of the topics that serve as the basis for Barrett's attacks, demonstrating that Barrett simply does not have scientific proof for his arguments; Gary Null does.

Who Is Stephen Barrett?

Stephen Barrett is a retired Psychiatrist who administers and operates Quackwatch.com, a website described by Donna Ladd of the Village Voice as "a skeptical psychiatrist's attempt to torpedo alternative and natural-health movements."

Barrett believes most alternative therapies simply should be disregarded without further research. "A lot of things don't need to be tested [because] they simply don't make any sense," he says, pointing specifically to homeopathy, chiropractic, and acupuncture. He believes that consumers

should rely solely on established medical groups and studies, and that anyone who wants to consider info on both sides is "waiting to be quacked in a major way."

Is Barrett Credible?

The California State Superior Court would answer this question with an emphatic "no". Stephen Barrett has presented his opinion and has staked personal credibility before the courts, on several occasions. In each instance, he has been made to suffer an embarrassingly unfavorable ruling.

In 2003, The Quackwatch flagship, known as the National Council Against Health Fraud (NCAHF) brought suit against 43 "Alternative Medicine proponents" in California, claiming that they were engaging in health fraud "because what they were doing wasn't scientifically proven." The ruling, which arrived on April 22, 2003, bludgeoned the NCAHF, and ripped apart their argument concerning what constitutes legitimate and effective health care.

The Court also declared that Stephen Barrett "was found to be biased and unworthy of credibility." In, 2005, Stephen Barrett's defamation lawsuit against Pennsylvania-based chiropractor, lecturer, researcher and publisher Ted Koren was tossed out by a judge just minutes before it was going to be considered by a local jury. The lawsuit, filed in August 2002, sought unspecified damages against Koren and his company, Koren Publications, Inc. for statements that he wrote in his newsletter in 2001 about Barrett.

In a landmark 2006 case, originally known as Barrett v. Clark, then for the appeals process renamed Barrett v. Rosenthal, the California Supreme Court voted unanimously to reject a libel claim filed by Barrett. His personal bias against alternative medicine was made unquestionably clear, as stated in the judge's ruling: "Plaintiffs Stephen Barrett and Terry Polevoy are physicians primarily engaged in combating the promotion and use of 'alternative' or 'nonstandard' healthcare practices and products."

Barrett's attacks on Gary Null, Ph.D

CNN, The New York Times, and other traditional, highly esteemed news outlets frequently cite Stephen Barrett as an expert in the discussion of the effectiveness and validity of Alternative Health, be it acupuncture, homeopathy, nutritional support, or chiropractic. Barrett's primary strategy in his campaign is to attack, and in certain cases, bring suit against, key members and

pillars of the alternative health movement. One such target is Dr. Gary Null. Barrett's claims that Null "promotes hundreds of ideas that are inaccurate, unscientific, and/or unproven..." are plainly false. Amongst those ideas are that the intake of Fluoride is harmful and potentially deadly, and that mercury in dental fillings can have serious neurotoxic effects. Dr. Null has also consistently warned of the harmful impact of sugar and the negative effects of caffeine. All of his observations and conclusions are supported by extensive, peer reviewed research and hard-won scientific scholarship. This approach stands in stark contrast to Barrett's own fast and loose, "things don't need to be tested [because] they simply don't make any sense" methodology.

Barrett has stated outright that Null should not be trusted or believed in his statements because he lacks a qualified degree. On his site, Barrett attacks Null's academic history. Sufficient documentation exists demonstrating that The Union Institute is not only accredited (http://en.wikipedia.org/wiki/The_Higher_Learning_Commission) and highly respected, but the university thought so highly of Null, that he was given the first Outstanding Alumni award ever offered by the college. At The Institute of Biology, he completed a landmark study on choleric restriction in rats, demonstrating a 22% extenuation of life span. Null has originated and completed dozens of studies in his nearly 30 year association with the institute. Additionally, Null has conducted more than 27 clinical trials on lifestyle and behavior modification and it's impact on health. Results of these studies, all of which were medically monitored, conclusively prove benefit to the top study group members, the results of which have all been published. Null is also a registered dietitian and nutritionist. To this journalist's amazement, after counseling tens of thousands, has never charged a penny to any person.

Barrett's Dilemma

There is presently a concerted effort within the alternative health movement to take Barrett to task for his tendency to pass subjective opinion off as scientific fact. In a written correspondence between Barrett's attorney Michael K. Botts, and Null's attorney David Slater, Botts concedes that Barrett's statements against Null were simply "a matter of opinion."

"He seems to be putting down trying to be objective," says Peter Barry Chowka, a former adviser to the National Institutes of Health's Office of Alternative Medicine. "Quackwatch.com is consistently provocative and entertaining" Chowka added. "But I personally think he's running against the tide of history. But that's his problem, not ours."

Final Conclusions

I can conclude that with absolute proof of an outstanding educational background, and his extensive clinical experience, that Gary Null is being attacked for what he represents: a viable challenge to the existing medical paradigm.

Supporting Research Documentation and Sources

REGARDING MERCURY, AMALGAM FILLINGS AND THYMEROSAL

1. MERCURY IN FILLINGS AND IMMUNIZATIONS

J Occup Med Toxicol. 2011 Jan 13;6(1):2.

Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission.

Mutter J.

Source

Department of Environmental and integrative medicine Lohnerhofstraße 2, 78467 Constance/Germany. jm@zahnklinik.de.

Abstract

It was claimed by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) in a report to the EU-Commission that "...no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease..." [1, available from: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_016.pdf]. SCENIHR disregarded the toxicology of mercury and did not include most important scientific studies in their review. But the real scientific data show that:(a) Dental amalgam is by far the main source of human total mercury body burden. This is proven by autopsy studies which found 2-12 times more mercury in body tissues of individuals with dental amalgam. Autopsy studies are the most valuable and most important studies for examining the amalgam-caused mercury body burden.(b) These autopsy studies have shown consistently that many individuals with amalgam have toxic levels of mercury in their brains or kidneys.(c) There is no correlation between mercury levels in blood or urine, and the levels in body tissues or the severity of clinical symptoms. SCENIHR only relied on levels in urine or blood. (d) The half-life of mercury in the brain can last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. However, SCENIHR state that the half-life of mercury in the body is only "20-90 days".(e) Mercury vapor is about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals.(f) Most studies cited by SCENIHR which conclude that amalgam fillings are safe have severe methodical flaws.

2. J Occup Med Toxicol. 2011 Jan 13;6(1):2.

Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission.

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**Department of Environmental and integrative medicine Lohnerhofstraße 2,
78467 Constance/Germany. jm@zahnklinik.de.**

Abstract

ABSTRACT: It was claimed by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) in a report to the EU-Commission that "...no risks of adverse systemic effects exist and the current use of dental amalgam does not pose a risk of systemic disease..." [1, available from: http://ec.europa.eu/health/ph_risk/committees/04_scenihr/docs/scenihr_o_016.pdf]. SCENIHR disregarded the toxicology of mercury and did not include most important scientific studies in their review. But the real scientific data show that: (a) Dental amalgam is by far the main source of human total mercury body burden. This is proven by autopsy studies which found 2-12 times more mercury in body tissues of individuals with dental amalgam. Autopsy studies are the most valuable and most important studies for examining the amalgam-caused mercury body burden. (b) These autopsy studies have shown consistently that many individuals with amalgam have toxic levels of mercury in their brains or kidneys. (c) There is no correlation between mercury levels in blood or urine, and the levels in body tissues or the severity of clinical symptoms. SCENIHR only relied on levels in urine or blood. (d) The half-life of mercury in the brain can last from several years to decades, thus mercury accumulates over time of amalgam exposure in body tissues to toxic levels. However, SCENIHR state that the half-life of mercury in the body is only "20-90 days". (e) Mercury vapor is about ten times more toxic than lead on human neurons and with synergistic toxicity to other metals. (f) Most studies cited by SCENIHR which conclude that amalgam fillings are safe have severe methodical flaws.

Swed Dent J. 1987;11(5):179-87.

3. Mercury concentrations in the human brain and kidneys in relation to exposure from dental amalgam fillings.

Nylander M, Friberg L, Lind B.

Source Department of Environmental Hygiene, Karolinska Institute, Sweden.

Abstract

Samples from the central nervous system (occipital lobe cortex, cerebellar cortex and ganglia semilunare) and kidney cortex were collected from autopsies and analysed for total mercury content using neutron activation analyses. Results from 34 individuals showed a statistically significant regression between the number of tooth surfaces containing amalgam and concentration of mercury in the occipital lobe cortex (mean 10.9, range 2.4-28.7 ng Hg/g wet weight). The regression equation $y = 7.2 + 0.24x$ has a 95% confidence interval for the regression coefficient of 0.11-0.37. In 9 cases with suspected alcohol abuse mercury levels in the occipital lobe were, in most cases, somewhat lower than expected based on the regression line. The observations may be explained by an inhibition of oxidation of mercury vapour. The regression between amalgams and mercury levels remained after exclusion of these cases. The kidney cortex from 7 amalgam carriers (mean 433, range 48-810 ng Hg/g wet weight) showed on average a significantly higher mercury level than those of 5 amalgam-free individuals (mean 49, range 21-105 ng Hg/g wet weight). In 6 cases analysis of both inorganic and total mercury was carried out. A high proportion (mean 77% SD 17%) of inorganic mercury was found. It is concluded that the cause of the association between amalgam load and accumulation of mercury in tissues is the release of mercury vapour from amalgam fillings.

4. Zentralbl Hyg Umweltmed. 1996 Feb;198(3):275-91.

[Study on the significance of mercury accumulation in the brain from

dental amalgam fillings through direct mouth-nose-brain transport].

[Article in German]

Maas C, Brück W, Haffner HT, Schweinsberg F.

Source Abteilung Allgemeine Hygiene und Umwelthygiene, Hygiene-Institut der Universität Tübingen.

Abstract

The transport of mercury (Hg) from the oro-nasal to the cranial cavity via a direct route was investigated. In 55 deceased persons, Hg concentrations were measured in the olfactory bulb and the trigeminal ganglion, and the number of dental amalgam fillings was assessed. For the purpose of comparison, Hg concentrations were also determined in the occipital lobe cortex, the pituitary gland and the kidney cortex. Quantitative Hg analysis was performed by cold vapor atomic absorption spectroscopy after acid digestion using high pressure microwave treatment. In the olfactory bulb (geom. mean 17.4 micrograms/kg w. w.), the Hg concentration was significantly higher than in the occipital lobe cortex (geom. mean 9.2 micrograms/kg w. w.) ($p < 0.0001$). No significant difference was found between the Hg concentration in the trigeminal ganglion (geom. mean 12 micrograms/kg w. w.) and the occipital lobe cortex ($\alpha = 0.005$; $p = 0.0342$). Regression analysis did not reveal a statistically significant correlation between the number of dental amalgam fillings and the Hg content in the olfactory bulb and the trigeminal ganglion, respectively ($\alpha = 0.01$). Therefore, these results do not support the hypothesis of a significant flow of Hg from dental amalgam fillings to the cranial cavity by a direct oro-nasal route. In contrast, a statistically significant correlation exists between the number of dental amalgam fillings and the Hg concentration in the kidney cortex ($r^2 = 0.317$; $p < 0.0001$), and, to a lesser extent, the Hg concentration in the occipital lobe cortex ($r^2 = 0.17$; $p = 0.0016$). The highest Hg concentrations (geom. mean 93.1 micrograms/kg w. w.) were detected in the kidney cortex, followed by the pituitary gland (geom. mean 30.0 micrograms/kg w. w.). In this study, Hg concentration in the pituitary gland did not correlate with the number of dental amalgam fillings.

5. Swed Dent J. 1989;13(6):235-43.

Mercury accumulation in tissues from dental staff and controls in relation to exposure.

Nylander M, Friberg L, Eggleston D, Björkman L.

Source

Department of Environmental Hygiene, Karolinska Institute, Stockholm, Sweden.

Abstract

Samples, mainly from occipital cortex and pituitary gland, but also from renal cortex, olfactory bulbs, thyroid gland and liver were collected from autopsies of 8 dental staff cases and 27 controls. These samples were analysed for total mercury content using radiochemical neutron activation analyses. The results revealed high mercury concentrations (median 815, range 135-4,040 micrograms Hg/kg wet weight) in pituitaries from the dental staff cases compared to controls (N = 23, median 23 range 6-1, 170 micrograms Hg/kg). In occipital cortex, the cases had a median of 17, range of 4-300 micrograms Hg/kg and the controls (N = 20) had a median of 10, range 2-29 micrograms Hg/kg. A few samples from olfactory bulbs show low mercury concentrations for both cases and controls. Renal cortex was analysed from three cases and contained clearly higher concentrations (945, 1,545, 2,110 micrograms Hg/kg) compared to controls (N = 12, median 180, range 21-810 micrograms Hg/kg). There is no control material for the other analysed samples, but one thyroid sample had an extremely high concentration of 28,000 micrograms Hg/kg.

6. Environ Health. 2007 Oct 11;6:30.

Mercury in human brain, blood, muscle and toenails in relation to exposure: an autopsy study.

Björkman L, Lundekvam BF, Laegreid T, Bertelsen BI, Morild I, Lilleng P, Lind B, Palm B, Vahter M.

Source Dental Biomaterials Adverse Reaction Unit, Department of Health/ UNIFOB, Arstadveien 17, NO-5009 Bergen, Norway.

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Abstract

BACKGROUND:

The main forms of mercury (Hg) exposure in the general population are methylmercury (MeHg) from seafood, inorganic mercury (I-Hg) from food, and mercury vapor (Hg⁰) from dental amalgam restorations. While the distribution of MeHg in the body is described by a one compartment model, the distribution of I-Hg after exposure to elemental mercury is more complex, and there is no biomarker for I-Hg in the brain. The aim of this study was to elucidate the relationships between on the one hand MeHg and I-Hg in human brain and other tissues, including blood, and on the other Hg exposure via dental amalgam in a fish-eating population. In addition, the use of blood and toenails as biological indicator media for inorganic and organic mercury (MeHg) in the tissues was evaluated.

METHODS:

Samples of blood, brain (occipital lobe cortex), pituitary, thyroid, abdominal muscle and toenails were collected at autopsy of 30 deceased individuals, age from 47 to 91 years of age. Concentrations of total-Hg and I-Hg in blood and brain cortex were determined by cold vapor atomic fluorescence spectrometry and total-Hg in other tissues by sector field inductively coupled plasma-mass spectrometry (ICP-SFMS).

RESULTS:

The median concentrations of MeHg (total-Hg minus I-Hg) and I-Hg in blood were 2.2 and 1.0 microg/L, and in occipital lobe cortex 4 and 5 microg/kg, respectively. There was a significant correlation between MeHg in blood and occipital cortex. Also, total-Hg in toenails correlated with MeHg in both blood and occipital lobe. I-Hg in both blood and occipital cortex, as well as total-Hg in pituitary and thyroid were strongly associated with the number of dental amalgam surfaces at the time of death.

CONCLUSION:

In a fish-eating population, intake of MeHg via the diet has a marked impact on the MeHg concentration in the brain, while exposure to dental amalgam restorations increases the I-Hg concentrations in the brain. Discrimination between mercury species is necessary to evaluate the impact on Hg in the brain of various sources of exposure, in particular, dental amalgam exposure.

7. Rev Environ Contam Toxicol. 2009;198:111-32.

Human health effects of methylmercury exposure.

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Source Environmental Chemistry Department, IDAEA-CSIC, Jordi Girona, 18-26, E-08034, Barcelona, Spain.

Abstract

Mercury (Hg), and the organometallic compounds formed from it, are among the most toxic of substances to the global environment. Mercury is environmentally ubiquitous, and both wildlife and humans are exposed to the toxic

effects of its environmental residues, primarily elemental mercury (Hg⁰), divalent mercury (Hg²⁺) and methylmercury (MeHg). Humans are exposed to different forms of Hg, and potential health risks have been reported from such exposures; examples of Hg exposure include mercury vapor from dental amalgams, occupational exposures and exposures during artisan and small-scale gold mining operations. Despite the significance of those foregoing Hg exposures, of particular concern is human and wildlife exposure to MeHg, a potent neurotoxicant. Once incorporated into the body, MeHg easily penetrates the blood-brain barrier and causes damage to the central nervous system, particularly in fetuses. It bioaccumulates and biomagnifies in the aquatic food chain; consequently, fish and seafood consumption is the major pathway by which humans are exposed to MeHg. MeHg is the focus of this review. It adversely affects humans and is currently the subject of intense public health interest and worldwide concern. In this review, I summarize the sources and cycling of global mercury in the environment, pathways of exposure, toxicity and exposure evaluation, toxicokinetics, the common biomarkers to evaluate exposure and effects in populations, and finally review the nutritional risks and benefits from fish consumption.

Ambio. 2007 Feb;36(1):3-11.

8. Methylmercury exposure and health effects in humans: a worldwide concern.

Mergler D, Anderson HA, Chan LH, Mahaffey KR, Murray M, Sakamoto M, Stern AH; Panel on Health Risks and Toxicological Effects of Methylmercury.

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Abstract

The paper builds on existing literature, highlighting current understanding and identifying unresolved issues about MeHg exposure, health effects, and risk assessment, and concludes with a consensus statement.

Methylmercury is a potent toxin, bioaccumulated and concentrated through the aquatic food chain, placing at risk people, throughout the globe and across the socioeconomic spectrum, who consume predatory fish or for whom fish is a dietary mainstay. Methylmercury developmental neurotoxicity has constituted the basis for risk assessments and public health policies. Despite gaps in our knowledge on new bioindicators of exposure, factors that influence MeHg uptake and toxicity, toxicokinetics, neurologic and cardiovascular effects in adult populations, and the nutritional benefits and risks from the large number of marine and freshwater fish and fish-eating species, the panel concluded that to preserve human health, all efforts need to be made to reduce and eliminate sources of exposure.

Int J Environ Res Public Health. 2010 Sep;7(9):3467-77. Epub 2010 Sep 16.

Research into mercury exposure and health education in subsistence fish-eating communities of the Amazon basin: potential effects on public health policy.

Dórea JG.

Source Department of Nutrition, Universidade de Brasília, P.O. Box 04322, Brasília, DF 70919-970, Brasil. dorea@rudah.com.br

Abstract

The neurotoxic effects of fish-methylmercury (meHg) consumed regularly are considered hazardous to fetuses and newborn infants; as a result fish consumption advisories are an important asset to control meHg exposure in

affluent societies. These concerns are now part of health promotion programs for Amazon subsistence villagers. While urban dwellers in affluent societies can choose an alternative nutritious diet, traditional and subsistence communities are caught up in controversial issues and lifestyle changes with unintended health consequences. Traditional fish-eating populations of industrialized and non-industrialized regions may be exposed to different neurotoxic substances: man-made pollutants and environmentally occurring meHg. Additionally, in non-industrialized countries, pregnant women and infants are still being immunized with thimerosal-containing vaccines (TCVs) which degrade to ethylmercury (etHg). Therefore, the complexity involving fish-meHg associated with wild-fish choices and Hg exposure derived from TCVs is difficult to disentangle and evaluate: are villagers able to distinguish exposure to differently hazardous chemical forms of Hg (inorganic, fish-meHg, and injected etHg)? Is it possible that instead of helping to prevent a plausible (unperceived) fish-meHg associated neurocognitive delay we may inadvertently arouse panic surrounding Hg exposure and disrupt subsistence fish-eating habits (necessary for survival) and life-saving vaccination programs (required by public health authorities)? These questions characterize the incompleteness of information related on the various chemical forms of Hg exposure and the need to convey messages that do not disrupt nutritional balance and disease prevention policies directed at Amazonian subsistence communities.

9. Methylmercury poisoning: Long-term clinical, radiological, toxicological, and pathological studies of an affected family

Annals of Neurology

Volume 35, Issue 6, pages 680–688, June 1994

Dr. Larry E. Davis MD1,6,* , Mario Kornfeld7, Herbert S. Mooney MD7, Kurt J. Fiedler MD2,6, Kathleen Y. Haaland PhD3,4,6,8, William W. Orrison MD5,9, Elsa Cernichiari MS10, Thomas W. Clarkson PhD10

Article first published online: 8 OCT 2004

DOI: 10.1002/ana.410350608

Abstract

For 3 months in 1969 a family in the United States that included a pregnant mother consumed pork containing methylmercury. Children, aged 20, 13, and 8 years and a neonate, developed severe neurological signs. Twenty-two years later, the 2 oldest had cortical blindness or constricted visual fields, diminished hand proprioception, choreoathetosis, and attentional deficits. Magnetic resonance images showed tissue loss in the calcarine and parietal cortices and cerebellar folia. The youngest had quadriplegia, blindness, and severe mental retardation until their deaths. The brain of the 8-year-old who died at age 30 showed cortical atrophy, neuronal loss, and gliosis, most pronounced in the paracentral and parietooccipital regions. The total mercury level in formalin-fixed, left occipital cortex was 1,974 ng/gm as measured by atomic absorption. Regional brain mercury levels correlated with extent of brain damage. A control patient had 38.5 ng of mercury/gm in the occipital cortex. Systemic organs in the patient and a control subject had comparable mercury levels. In mercury-intoxicated rats, we found that only 5 to 10% of total brain mercury was lost by formalin fixation. Brain inorganic mercury in the patient ranged from 82 to 100%. Since inorganic mercury crosses the blood-brain barrier poorly, biotransformation of methyl to inorganic mercury may have occurred after methylmercury crossed the blood-brain barrier, accounting for its persistence in brain and causing part of the brain damage.

10. Acta Neuropathologica

Volume 20, Number 4, 316-334, DOI: 10.1007/BF00691749

Original Investigations

Ultrastructural studies of the nervous system after mercury intoxication

Louis W. Chang and Henrik A. Hartmann

Abstract

Mercury was first detected histochemically in the Schwann cells between 12 and 24 h after the administration of organic or inorganic mercury compound. After 4 days of intoxication, mercury could be observed in the axoplasm. Pathological changes in the dorsal root fibers were observed 1 week after CH₃HgCl and 2 weeks after HgCl₂ intoxication.

After HgCl₂ poisoning, a large axonal space was created in many axons as a result of detachment of the axolemma from the myelin sheath and axonal shrinkage. Axonal degeneration, vacuolation, and collapse were observed in many nerve fibers. Although myelin destruction could be observed occasionally, the regular lamination and periodicity of the myelin sheath were usually preserved.

After CH₃HgCl poisoning, however, the myelin sheaths seemed to have lost their lamination and have a smudged or solid appearance. Extensive axoplasmic degeneration, axonal collapse, and myelin destruction were the most prominent lesions observed in these nerve fibers.

Pathological changes in the ventral root fibers and sciatic nerve were not observed until the second week of intoxication by either organic or inorganic mercury compound. While only limited damages were produced in the ventral root fibers, extensive degradation of the axons and demyelination of the nerve fibers were observed in the sciatic nerve.

Disoriented layering of myelin to form concentric myelin structures and active phagocytosis of the degenerative debris by the reactive Schwann cells were also observed.

11. MEDICAL HYPOTHESES

Volume 56, Issue 4, Pages 462-471 (April 2001)

Autism: a novel form of mercury poisoning

S. Bernard, A. Enayati, L. Redwood, H. Roger, T. Binstock

Received 3 July 2000; accepted 22 December 2000.

Abstract

Autism is a syndrome characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recent epidemiological studies suggest that autism may affect 1 in 150 US children. Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children.

12. Neurobehavioral effects from exposure to dental amalgam Hgo: new distinctions between recent exposure and Hg body burden

Diana Echeverria^{a,b,1}, H. Vasken Aposhian^c, James S. Woods^{a,b}, Nicholas J. Heyer^b, Mary M. Aposhian^c, Alvah C. Bittner, JR.^{a,b}, Roderick K. Mahurin, and Margaret Cianciolad

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Potential toxicity from exposure to mercury vapor (Hgo) from dental amalgam fillings is the subject of current public health debate in many countries. We evaluated potential central nervous system (CNS) toxicity associated with handling Hg-containing amalgam materials among dental personnel with very low levels of Hgo exposure (i.e., urinary Hg <4 µg/l), applying a neurobehavioral test battery to evaluate CNS functions in relation to both recent exposure and Hg body burden. New distinctions between subtle preclinical effects on symptoms, mood, motor function, and cognition were found associated with Hg body burden as compared with those associated with recent exposure. The pattern of results, comparable to findings previously reported among subjects with urinary Hg >50 µg/l, presents convincing new evidence of adverse behavioral effects associated with low Hgo exposures within the range of that received by the general population.—Echeverria, D., Aposhian, H. V., Woods, J. S., Heyer, N. J., Aposhian, M. M., Bittner, A. C., Jr., Mahurin, R. K. Neurobehavioral effects from exposure to dental amalgam Hgo: new distinctions between recent exposure and Hg body burden. *FASEB J.* 12, 971–980 (1998)

13. J Toxicol Environ Health A. 2009;72(14):891-6.

Urinary porphyrin excretion in children with mercury amalgam treatment: findings from the Casa Pia Children's Dental Amalgam Trial.

Woods JS, Martin MD, Leroux BG, DeRouen TA, Bernardo MF, Luis HS, Leitão JG, Simmonds PL, Echeverria D, Rue TC.

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Abstract

Increases in the urinary concentrations of pentacarboxyl- and coproporphyrins and the appearance of the atypical precoproporphyrin have been defined in relation to mercury (Hg) body burden in animal studies, and this change in the porphyrin excretion pattern has been described as a biomarker of occupational Hg exposure and toxicity in adult human subjects. In the present studies, urinary porphyrins were determined in relation to Hg exposure in children and adolescents, 8-18 yr of age, over the 7-yr course of a clinical trial designed to evaluate the neurobehavioral and renal effects of dental amalgam in children. Subjects were randomized to either dental amalgam or composite resin treatments. Urinary porphyrins and creatinine concentrations were measured at baseline and annually in all subjects. Results were evaluated using linear regression analysis. No significant differences between treatment groups (amalgam versus composite) were found when comparing all subjects for any of the porphyrins of interest. However, incipient amalgam treatment-specific increases were observed in the mean concentrations of penta-, precopro- and coproporphyrins especially when the analyses were restricted to younger subjects (8 to 9 yr old at baseline), and these increases were most apparent during yr 2 through 3 of follow-up, the period of highest mercury exposure from amalgam treatment. Based on the mean number of amalgam fillings received by children in this group (17.8), the renal Hg concentration associated with incipient increases in urinary porphyrins was estimated to be approximately 2.7 microg/g renal cortex. This value corresponds to an observed mean urinary Hg concentration of 3.2 microg/g creatinine, which is approximately fivefold less than that at which renal damage from Hg exposure is estimated to occur in children. These findings are consistent with growing evidence supporting the sensitivity of urinary porphyrins as a biological indicator of subclinical Hg exposure in children.

14. Environ Health Perspect. 2007 Oct;115(10):1527-31.

The contribution of dental amalgam to urinary mercury excretion in children.

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Abstract

BACKGROUND:

Urinary mercury concentrations are widely used as a measure of mercury exposure from dental amalgam fillings. No studies have evaluated the relationship of these measures in a longitudinal context in children.

OBJECTIVE:

We evaluated urinary mercury in children 8-18 years of age in relation to number of amalgam surfaces and time since placement over a 7-year course of amalgam treatment.

METHODS:

Five hundred seven children, 8-10 years of age at baseline, participated in a clinical trial to evaluate the neurobehavioral effects of dental amalgam in children. Subjects were randomized to either dental amalgam or resin composite treatments. Urinary mercury and creatinine concentrations were measured at baseline and annually on all participants.

RESULTS:

Treatment groups were comparable in baseline urinary mercury concentration (approximately 1.5 microg/L). Mean urinary mercury concentrations in the amalgam group increased to a peak of approximately 3.2 microg/L at year 2 and then declined to baseline levels by year 7 of follow-up. There was a strong, positive association between urinary mercury and both number of amalgam surfaces and time since placement. Girls had significantly higher mean urinary mercury concentrations than boys throughout the course of amalgam treatment. There were no differences by race in urinary mercury concentration associated with amalgam exposure.

CONCLUSIONS:

Urinary mercury concentrations are highly correlated with both number of amalgam fillings and time since placement in children. Girls excrete significantly higher concentrations of mercury in the urine than boys with comparable treatment, suggesting possible sex-related differences in mercury handling and susceptibility to mercury toxicity.

15. J Dent Res. 2003 Mar;82(3):243-6.

Neurotoxicity of dental amalgam is mediated by zinc.

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Abstract

The use of dental amalgam is controversial largely because it contains mercury. We tested whether amalgam caused toxicity in neuronal cultures and whether that toxicity was caused by mercury. In this study, we used cortical cell cultures to show for the first time that amalgam causes nerve cell toxicity in culture. However, the toxicity was not blocked by the mercury chelator, 2,3-dimercaptopropane-1-sulphonate (DMPS), but was blocked by the metal chelator, calcium disodium ethylenediaminetetraacetate (CaEDTA). DMPS was an effective mercury chelator in this system, since it blocked mercury toxicity. Of the components that comprise amalgam (mercury, zinc, tin, copper, and silver), only zinc neurotoxicity was blocked by CaEDTA. These results indicate that amalgam is toxic to nerve cells in culture by releasing zinc. While zinc is known to be neurotoxic, ingestion of zinc is not a major concern because zinc levels in the body are tightly regulated.

REGARDING SUGAR CONSUMPTION

(Circulation. 2009;120:1011-1020.)

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17. Dietary Sugars Intake and Cardiovascular Health A Scientific Statement From the American Heart Association

Rachel K. Johnson, PhD, MPH, RD, Chair; Lawrence J. Appel, MD, MPH, FAHA; Michael Brands, PhD, FAHA; Barbara V. Howard, PhD, FAHA; Michael Lefevre, PhD, FAHA; Robert H. Lustig, MD; Frank Sacks, MD, FAHA; Lyn M. Steffen, PhD, MPH, RD, FAHA; Judith Wylie-Rosett, EdD, RD, on behalf of the American Heart Association Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism and the Council on Epidemiology and Prevention

High intakes of dietary sugars in the setting of a worldwide pandemic of obesity and cardiovascular disease have heightened concerns about the adverse effects of excessive consumption of sugars. In 2001 to 2004, the usual intake of added sugars for Americans was 22.2 teaspoons per day (355 calories per day). Between 1970 and 2005, average annual availability of sugars/added sugars increased by 19%, which added 76 calories to Americans' average daily energy intake. Soft drinks and other sugar-sweetened beverages are the primary source of added sugars in Americans' diets. Excessive consumption of sugars has been linked with several metabolic abnormalities and adverse health conditions, as well as shortfalls of essential nutrients. Although trial data are limited, evidence from observational studies indicates that a higher intake of soft drinks is associated with greater energy intake, higher body weight, and lower intake of essential nutrients. National survey data also indicate that excessive consumption of added sugars is contributing to overconsumption of discretionary calories by Americans. On the basis of the 2005 US Dietary Guidelines, intake of added sugars greatly exceeds discretionary calorie allowances, regardless of energy needs. In view of these considerations, the American Heart Association recommends reductions in the intake of added sugars. A prudent upper limit of intake is half of the discretionary calorie allowance, which for most American women is no more than 100 calories per day and for most American men is no more than 150 calories per day from added sugars.

18. Sweet and salty: nutritional content and analysis of baby and toddler foods

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Abstract

Background To critically examine baby and toddler food products sold in Canada for their sugar and sodium content, and to assess these in light of current recommendations.

Methods Baby and toddler foods (n = 186) were coded for various attributes, including 'Nutrition Facts' label data. Four 'categories' of baby/toddler foods were analyzed against their 'adult' counterparts for sugar and salt to reveal whether a 'halo effect' attributed to baby/toddler food is warranted.

Results 63% of products have either high levels of sodium or an excessive proportion of calories coming from sugar. Over 12% of products had moderate or high levels of sodium; over 53% of products derive >20% of their calories from sugar. Baby and toddler foods were not found to be nutritionally superior—in terms of sodium or sugar—to their adult counterparts.

Conclusions Baby and toddler foods are currently overlooked in the public, and public policy, discussions pertaining to dietary sodium and sugar. Yet these products are clearly of concern and should be closely monitored, since they promote a taste for 'sweet' and 'salty' in our youngest consumers.

19. Effects of Serving High-Sugar Cereals on Children's Breakfast-Eating Behavior

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Abstract

OBJECTIVES: To test (1) whether children will consume low-sugar ready-to-eat (RTE) cereals and (2) the effects of serving high- versus low-sugar cereals on the consumption of cereal, refined sugar, fresh fruit, and milk.

PARTICIPANTS AND METHODS: Using an experimental design, we randomly assigned children (n = 91) who were attending summer day camp to receive a breakfast that included either the choice of 1 of 3 high-sugar cereals (high-sugar condition) or low-sugar cereals (low-sugar condition), as well as low-fat milk, orange juice, bananas, strawberries, and sugar packets. Participants served themselves and completed a background questionnaire after eating. Researchers measured the amount and calories consumed of each food.

RESULTS: In both conditions, children reported "liking" or "loving" the cereal they chose. Children in the low-sugar cereal condition consumed, on average, slightly more than 1 serving of cereal (35 g), whereas children in the high-sugar condition consumed significantly more (61 g) and almost twice the amount of refined sugar in total (24.4 vs 12.5 g). Milk and total calories consumed did not differ significantly between conditions, but children in the low-sugar condition were more likely to put fruit on their cereal (54% vs 8%) and consumed a greater portion of total calories from fresh fruit (20% vs 13%).

CONCLUSIONS: Compared with serving low-sugar cereals, high-sugar cereals increase children's total sugar consumption and reduce the overall nutritional quality of their breakfast. Children will consume low-sugar cereals when offered, and they provide a superior breakfast option.

20. Hypertension. 2011;57:695-701

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HYPERTENSIONAHA.110.165456
Population Science/Epidemiology

Sugar-Sweetened Beverage, Sugar Intake of Individuals, and Their Blood Pressure
International Study of Macro/Micronutrients and Blood Pressure
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The obesity epidemic has focused attention on relationships of sugars and sugar-sweetened beverages (SSBs) to cardiovascular risk factors. Here we report cross-sectional associations of SSBs, diet beverages, and sugars with blood pressure (BP) for United Kingdom and US participants of the International Study of Macro/Micronutrients and Blood Pressure. Data collected include four 24-hour dietary recalls, two 24-hour urine collections, 8 BP readings, and questionnaire data for 2696 people ages 40 to 59 years of age from 10 US/United Kingdom population samples. Associations of SSBs, diet beverages, and sugars (fructose, glucose, and sucrose) with BP were assessed by multiple linear regression. SSB intake related directly to BP, with P values of 0.005 to <0.001 (systolic BP) and 0.14 to <0.001 (diastolic BP). SSB intake higher by 1 serving per day (355 mL/24 hours) was associated with systolic/diastolic BP differences of +1.6/+0.8 mm Hg (both P<0.001) and +1.1/+0.4 mm Hg (P<0.001/<0.05) with adjustment for weight and height. Diet beverage intake was inversely associated with BP (P 0.41 to 0.003). Fructose- and glucose-BP associations were direct, with significant sugar-sodium interactions: for individuals with above-median 24-hour urinary sodium excretion, fructose intake higher by 2 SD (5.6% kcal) was associated with systolic/diastolic BP differences of +3.4/+2.2 mm Hg (both P<0.001) and +2.5/+1.7 mm Hg (both P=0.002) with adjustment for weight and height. Observed independent, direct associations of SSB intake and BP are consistent with recent trial data. These findings, plus adverse nutrient intakes among SSB consumers, and greater sugar-BP differences for persons with higher sodium excretion lend support to recommendations that intake of SSBs, sugars, and salt be substantially reduced.

20. Circulation. 2011;123:249-257

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Epidemiology and Prevention

Consumption of Added Sugars and Indicators of Cardiovascular Disease Risk

Among US Adolescents

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Background— Whereas increased carbohydrate and sugar consumption has been associated with higher cardiovascular disease risk among adults, little is known about the impact of high consumption of added sugars (caloric sweeteners) among US adolescents.

Methods and Results— In a cross-sectional study of 2157 US adolescents in the National Health and Nutrition Examination Survey (NHANES) 1999 to 2004, dietary data from one 24-hour recall were merged with added sugar content data from the US Department of Agriculture MyPyramid Equivalents databases. Measures of cardiovascular disease risk were estimated by added sugar consumption level (<10%, 10 to <15%, 15 to <20%, 20 to <25%, 25 to <30%, and 30% of total energy). Multivariable means were weighted to be representative of US adolescents and variances adjusted for the complex sampling methods. Daily consumption of added sugars averaged 21.4% of total energy. Added sugars intake was inversely correlated with mean high-density lipoprotein cholesterol levels (mmol/L) which were 1.40 (95% confidence interval [CI] 1.36 to 1.44) among the lowest consumers and 1.28 (95% CI 1.23 to 1.33) among the highest (P trend =0.001). Added sugars were positively correlated with low-density lipoproteins (P trend =0.01) and geometric mean triglycerides (P trend =0.05). Among the lowest and highest consumers, respectively, low-density lipoproteins (mmol/L) were 2.24 (95% CI 2.12 to 2.37) and 2.44 (95% CI 2.34 to 2.53), and triglycerides (mmol/L) were 0.81 (95% CI 0.74, 0.88) and 0.89 (95% CI 0.83 to 0.96). Among those overweight/obese (85th percentile body-mass-index), added sugars were positively correlated with the homeostasis model assessment (P linear trend =0.004).

Conclusion— Consumption of added sugars among US adolescents is positively associated with multiple measures known to increase cardiovascular disease risk.

21. Circulation. 2010;122:2470-2490

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AHA Conference Proceedings

**Translation and Implementation of Added Sugars Consumption Recommendations
A Conference Report From the American Heart Association Added Sugars
Conference 2010**

Linda Van Horn, PhD, RD, FAHA, Chair; Rachel K. Johnson, PhD, MPH, RD, Co-Chair; Brent D. Flickinger, PhD, Co-Chair; Dorothea K. Vafiadis, MS; Shirley Yin-Piazza, MS, MBA*, on behalf of the Added Sugars Conference Planning Group

Background— A 2-day forum was convened to (1) discuss ways to translate the 2009 American Heart Association added sugars recommendations into actions in areas such as regulation, food labeling, nutrient content claims, and practical application in the American diet; (2) review surveillance methodology and metrics for tracking and understanding the impact of reducing added sugars in the diet; and (3) initiate the development of a framework for future collaboration to help Americans implement science-based guidance relative to added sugars.

Methods and Results— More than 100 multinational participants representing scientists from academia and government and stakeholders engaged in food production, development, and processing, food manufacturing and servicing, food and nutrition policy, and nutrition recommendations for the public attended the conference. Presentations included definitions and examples of added sugars, current US and international added sugars perspectives, added sugars in diets of individuals and in the food supply, food technology behind added sugars, added sugars and health, food manufacturer perspectives, added sugars food-labeling considerations, and examples of positive approaches to improve eating behaviors and the food environment. Facilitated breakout sessions were conducted after the plenary sessions to allow participants to contribute their expertise and thoughts.

Conclusion— The American Heart Association Added Sugars Conference is the first step in an important process that facilitates collaboration across science, public health, and industry to foster innovation, partnerships, policy, and implementation of new products and services for the benefit of the health and well-being of the American public. Science has advanced in the area of added sugars and health, creating mounting pressure to use better methods for translation and dissemination of the science for consumer education and for food companies to respond by producing foods and beverages with fewer added sugars. The new science also reinforces the importance of preventing, rather than simply treating diseases, especially overweight and obesity, diabetes mellitus, high blood pressure, heart disease, and stroke. Reducing added sugars consumption is a good target for addressing obesity, along with other sources of excess calories. However, the potential unintended consequences of substituting added sugars with ingredients that may not reduce calories and of increasing other macronutrients or food groups that may not result in a net health gain must be considered. Although there are many challenges to incorporating added sugars to the food label as was discussed during the conference, disclosure of added sugars content on food and beverage labels is an essential element in consumer education and can provide the information and motivation for making healthier food choices. This conference demonstrated the value of interactive dialogue among multiple sectors and disciplines. More disciplines should be at the table to bring expertise to discuss cross-cutting issues related to public policies and offer diverse insights to finding a solution.

SAGE JOURNALS ONLINE

22. NUTRITION IN CLINICAL PRACTICE

The Standard American Diet and Its Relationship to the Health Status of Americans

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Abstract

The Standard American Diet (SAD) has long been implicated in contributing to the health challenges experienced in the United States. Significant changes to the SAD have occurred since the 1950s, including a greater abundance and accessibility to calorie-dense and nutrient-poor food and beverage choices. The disparity of present consumption patterns to diet and nutrition recommendations from the Dietary Guidelines for Americans are addressed.

AMERICAN DIABETES ASSOCIATION
DIABETES CARE

23. Sugar-Sweetened Beverages and Risk of Metabolic Syndrome and Type 2

Diabetes

A meta-analysis

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Abstract

OBJECTIVE Consumption of sugar-sweetened beverages (SSBs), which include soft drinks, fruit drinks, iced tea, and energy and vitamin water drinks has risen across the globe. Regular consumption of SSBs has been associated with weight gain and risk of overweight and obesity, but the role of SSBs in the development of related chronic metabolic diseases, such as metabolic syndrome and type 2 diabetes, has not been quantitatively reviewed.

RESEARCH DESIGN AND METHODS We searched the MEDLINE database up to May 2010 for prospective cohort studies of SSB intake and risk of metabolic syndrome and type 2 diabetes. We identified 11 studies (three for metabolic syndrome and eight for type 2 diabetes) for inclusion in a random-effects meta-analysis comparing SSB intake in the highest to lowest quantiles in relation to risk of metabolic syndrome and type 2 diabetes.

RESULTS Based on data from these studies, including 310,819 participants and 15,043 cases of type 2 diabetes, individuals in the highest quantile of SSB intake (most often 1–2 servings/day) had a 26% greater risk of developing type 2 diabetes than those in the lowest quantile (none or <1 serving/month) (relative risk [RR] 1.26 [95% CI 1.12–1.41]). Among studies evaluating metabolic syndrome, including 19,431 participants and 5,803 cases, the pooled RR was 1.20 [1.02–1.42].

CONCLUSIONS In addition to weight gain, higher consumption of SSBs is associated with development of metabolic syndrome and type 2 diabetes. These data provide empirical evidence that intake of SSBs should be limited to reduce obesity-related risk of chronic metabolic diseases.

AMERICAN JOURNAL OF PHYSIOLOGY
ENDOCRINOLOGY AND METABOLISM

24. Fructose: a highly lipogenic nutrient implicated in insulin resistance, hepatic steatosis, and the metabolic syndrome

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Abstract

As dietary exposure to fructose has increased over the past 40 years, there is growing concern that high fructose consumption in humans may be in part responsible for the rising incidence of obesity worldwide. Obesity is associated with a host of metabolic challenges, collectively termed the metabolic syndrome. Fructose is a highly lipogenic sugar that has profound metabolic effects in the liver and has been associated with many of the components of the metabolic syndrome (insulin resistance, elevated waist circumference, dyslipidemia, and hypertension). Recent evidence has also uncovered effects of fructose in other tissues, including adipose tissue, the brain, and the gastrointestinal system, that may provide new insight into the metabolic consequences of high-fructose diets. Fructose feeding has now been shown to alter gene expression patterns (such as peroxisome proliferator-activated receptor- γ coactivator-1 α/β in the liver), alter satiety factors in the brain, increase inflammation, reactive oxygen species, and portal endotoxin concentrations via Toll-like receptors, and induce leptin resistance. This review highlights recent findings in fructose feeding studies in both human and animal models with a focus on the molecular and biochemical mechanisms that underlie the development of insulin resistance, hepatic steatosis, and the metabolic syndrome.

26. THE JOURNALS OF GERONTOLOGY

SERIES A

Increased Fructose Intake as a Risk Factor For Dementia

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Received February 8, 2010.

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Abstract

The transition in the world age demographic toward older age is associated with an increased risk of neurodegenerative diseases, such as Alzheimer's disease. Risk profiles for dementia may also be changing. Obesity and type 2 diabetes have increased in prevalence in the last half-century and have been associated with increased dementia risk. Specific changes in nutrition may also represent a direct risk. A diet transition in the

United States has occurred in the intake of refined sugar, particularly high-fructose corn syrup (HFCS) from a yearly estimate of 8.1 kg/person at the beginning of the XIX century to a current estimate of 65 kg/person. This article considers the association between refined sugar intake, markers of cardiovascular disease risk, and the possible promotion of the development of dementia.

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Contemporary Reviews in Cardiovascular Medicine

Sugar-Sweetened Beverages, Obesity, Type 2 Diabetes Mellitus, and Cardiovascular Disease Risk

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INTRODUCTION

Obesity has recently emerged as a major global health problem. According to World Health Organization estimates, 1.6 billion adults worldwide were overweight (body mass index [BMI] 25 kg/m²) and at least 400 million were obese (BMI 30 kg/m²) in 2005, numbers that are expected to reach 2.3 billion and 700 million, respectively, by 2015. In the United States, the percentage of overweight and obese adults increased markedly from 47% and 15% in 1976 to 1980 to >66% and 33% in 2005 to 2006, with the greatest proportion of increase seen among non-Hispanic black and Mexican American women.^{1,2} The implications of excess body weight are far-reaching. Epidemiological studies indicate that overweight and obesity are important risk factors for type 2 diabetes mellitus (T2DM), cardiovascular disease, cancer, and premature death.³ In the United States, healthcare expenditures attributable to overweight and obesity are estimated to be \$147 billion or 9.1% of total healthcare costs per year.⁴ Such excess costs could have serious repercussions for resource-poor countries, which must manage the dual burdens of chronic and infectious disease.

In the setting of a pandemic of obesity and related chronic diseases, the American Heart Association recently released a scientific statement recommending reductions in added-sugar intake to no more than 100 to 150 kcal/d for most Americans.⁵ The statement identified sugar-sweetened beverages (SSBs) as the primary source of added sugars in the American diet.⁶ Although it has long been suspected that SSBs contribute at least in part to the obesity epidemic, only in recent years have large epidemiological studies been able to substantiate the relationship between SSB consumption and long-term weight gain, T2DM, and cardiovascular risk. It is thought that SSBs contribute to weight gain because of their high added-sugar content, low satiety, and potential

incomplete compensation for total energy, leading to increased energy intake.^{7,8} In addition, because of their high amounts of rapidly absorbable carbohydrates such as various forms of sugar and high-fructose corn syrup (HFCS) and the large quantities consumed, SSBs may increase T2DM and cardiovascular risk independently of obesity as a contributor to a high dietary glycemic load (GL), leading to inflammation, insulin resistance, and impaired β -cell function.⁹ Fructose from any sugar or HFCS may also increase blood pressure and promote the accumulation of visceral adiposity, dyslipidemia, and ectopic fat deposition because of increased hepatic de novo lipogenesis.¹⁰ Here, we review temporal patterns in SSB consumption and clinically relevant effects on obesity, T2DM, and cardiovascular disease risk, emphasizing potential underlying biological mechanisms, clinical implications, and consideration of methodological issues inherent in the literature.

28. Circulation. 2010;121:586-613

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AHA Special Report

Defining and Setting National Goals for Cardiovascular Health Promotion and Disease Reduction

The American Heart Association's Strategic Impact Goal Through 2020 and Beyond

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This document details the procedures and recommendations of the Goals and Metrics Committee of the Strategic Planning Task Force of the American Heart Association, which developed the 2020 Impact Goals for the organization. The committee was charged with defining a new concept, cardiovascular health, and determining the metrics needed to monitor it over time. Ideal cardiovascular health, a concept well supported in the literature, is defined by the presence of both ideal health behaviors (nonsmoking, body mass index <25 kg/m², physical activity at goal levels, and pursuit of a diet consistent with current guideline recommendations) and ideal health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure <120/<80 mm Hg, and fasting blood glucose <100 mg/dL). Appropriate levels for children are also provided. With the use of levels that span the entire range of the same metrics, cardiovascular health status for the whole population is defined as poor, intermediate, or ideal. These metrics will be monitored to determine the changing prevalence of cardiovascular health status and define achievement of the Impact Goal. In addition, the committee recommends goals for further reductions in cardiovascular disease and stroke mortality. Thus, the committee recommends the following Impact Goals: "By 2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%." These goals will require new strategic directions for the American Heart Association in its research, clinical, public health, and advocacy programs for cardiovascular health promotion and disease prevention in the next decade and beyond.

29. JOURNAL OF THE AMERICAN DENTAL ASSOCIATION

Diet, Cardiovascular Disease and Oral Health Promoting Health and Reducing Risk Riva Touger-Decker, PhD, RD, FADA

Abstract

Background. Primary prevention of cardiovascular disease includes screening as well as education and risk-reduction efforts.

Methods. The author reviewed diet and nutritional risk factors for cardiovascular disease (CVD), as well as dietary approaches to reduce the risk of developing CVD. The author also presented applications for use in dental practice.

Conclusions. The multifaceted relationship between diet/nutrition, CVD and oral health supports the role of CVD risk-reduction strategies in dental practice.

Clinical Implications. Reinforcement of healthful lifestyle principles may help reduce patients' risk of developing CVD and improve their systemic and oral health.

REGARDING CAFFEINE

<http://www.springerlink.com/content/wl412194360xj32t/abstract/?target=print>

Psychopharmacology

Volume 94, Number 4, 437-451, DOI: 10.1007/BF00212836

Reviews

30. Caffeine physical dependence: a review of human and laboratory animal studies

Roland R. Griffiths and Phillip P. Woodson

References (132)

Cited By (59)

Abstract

Although caffeine is the most widely used behaviorally active drug in the world, caffeine physical dependence has been poorly characterized in laboratory animals and only moderately well characterized in humans. In humans, a review of 37 clinical reports and experimental studies dating back to 1833 shows that headache and fatigue are the most frequent withdrawal symptoms, with a wide variety of other signs and symptoms occurring at lower frequency (e.g. anxiety, impaired psychomotor performance, nausea/vomiting and craving). When caffeine withdrawal occurs, severity can vary from mild to extreme (i.e. incapacitating). The withdrawal syndrome has an onset at 12–24 h, peak at 20–48 h, and duration of about 1 week. The pharmacological specificity of caffeine withdrawal has been established. The proportion of heavy caffeine users who will experience withdrawal symptoms has been estimated from experimental studies to range from 25% to 100%. Withdrawal symptoms have been documented after relatively short-term exposure to high doses of caffeine (i.e. 6–15 days of 600 mg/day). Although animal and human studies suggest that physical dependence may potentiate the reinforcing effects of caffeine, human studies also demonstrate that a history of substantial caffeine intake is not a necessary condition for caffeine to function as a reinforcer. The similarities and differences between caffeine and classic drugs of abuse are discussed.

Key words Caffeine - Caffeinism - Coffee - Tea - Physical dependence - Withdrawal - Reinforcer - Drug self-administration - Subjective effects - Drug dependence - Drug abuse - Humans - Animals

<http://www.sciencedirect.com/science?>

[ob=ArticleURL&udi=B6T2C-47NV7JV-7D&user=10&coverDate=12%2F31%2F1975&rdoc=1&fmt=high&orig=](http://www.sciencedirect.com/science?ob=ArticleURL&udi=B6T2C-47NV7JV-7D&user=10&coverDate=12%2F31%2F1975&rdoc=1&fmt=high&orig=)

gateway&_origin=gateway&_sort=d&_docanchor=&_view=c&_searchStrId=1739337287&_rerunOrigin=google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=b8cfe9e1f14a3ceda2a9777ed7f1b6ef&searchtype=a

31. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis

Volume 33, Issues 2-3, December 1975, Pages 279-284

Cited By in Scopus (8)

Post-replication repair of DNA in chinese hamster cells treated with CIS platinum (II) diamine dichloride. Enhancement of toxicity and chromosome damage by caffeine

H.W. Van Den Berga and J.J. Roberts

Institute of Cancer Research, Royal Cancer Hospital, Pollards Wood Research Station, Chalfont St. Giles, Bucks. England

Received 25 April 1975; revised 27 June 1975; accepted 25 July 1975. Available online 13 January 2003.

Abstract

The anti-tumor agent cis platinum (II) diammine dichloride (cis Pt(II)) caused chromosomal abnormalities in Chinese hamster V79–379A cells. The time of appearance of these abnormalities suggested that they arise as a consequence of DNA synthesis on a damaged template. The yield and severity of chromosomal abnormalities was greatly enhanced by a non-toxic concentration of caffeine, and this enhancement was associated with a potentiation of cis Pt(II) induced cell death.

These results suggest that damage to DNA which arises from cis Pt(II) treatment can be repaired in this cell line by a caffeine-sensitive post-replication repair process.

Abbreviations: cis Pt(II), cis platinum (II) diammine dichloride; DMSO, dimethylsulphoxide

http://www.caffeinedependence.org/caffeine_dependence.html

32. JOHNS HOPKINS
BAYVIEW
MEDICAL CENTER

INFORMATION ABOUT CAFFEINE DEPENDENCE

CAFFEINE AND HEALTH (excerpt)

“Caffeine use can be associated with several distinct psychiatric syndromes: caffeine intoxication, caffeine withdrawal, caffeine dependence, caffeine-induced sleep disorder, and caffeine-induced anxiety disorder. Studies have not proven that caffeine produces significant life-threatening health risks such as cancer, heart disease, and human reproduction abnormalities. Nevertheless, individuals

with various conditions such as generalized anxiety disorder, panic disorder, primary insomnia, gastroesophageal reflux, pregnancy and urinary incontinence are often advised to reduce or eliminate regular caffeine use. With regard to cardiovascular health, caffeine produces modest increases in blood pressure and studies have established that unfiltered caffeinated and decaffeinated coffee (including espresso and French Press) contain lipids which raise serum cholesterol. In addition, concerns have been raised about a role of caffeine in cardiovascular disease. Finally, studies suggest that there may be an association between high daily caffeine consumption and delayed conception and lower birth weight.”

<http://www.nrcresearchpress.com/doi/abs/10.1139/y67-033>

33. THE INFLUENCE OF SEX AND AGE IN ALBINO RATS GIVEN A DAILY ORAL DOSE OF CAFFEINE AT A HIGH DOSE LEVEL

Josef M. Peters, Eldon M. Boyd

Canadian Journal of Physiology and Pharmacology, 1967, 45:305-311, 10.1139/y67-033

Abstract

Caffeine was given daily for 14 days in an oral dose of 185 mg/kg to male and female albino rats in groups of increasing body weight. The sensitivity of rats to the lethal effects of caffeine increased with increase in age. Psychotoxic (auto-mutilation plus hemorrhage) deaths were most common in young rats, and hypokinetic–convulsive deaths in older animals. In survivors, the incidence of glycosuria and hydration of the kidneys was greater, and dehydration of the adrenal glands and gonads less, in older than in younger rats. Sublethal signs of toxicity in male survivors were greater than in female survivors. Anorexia and loss of body weight were greater in male than in female survivors, diuresis was less evident, loss of muscle weight was greater, and the relative gain in weight of the adrenal glands and gastrointestinal tract were greater. In brief, caffeine was found to be more toxic in older than in younger rats and in males than in females.

from <http://www.caffeineweb.com/>

34. Medscape: **“Patients who become caffeine-toxic may not even realize it.”**

“Too often, patients presenting with complaints of some form of anxiety do not have a careful caffeine history taken. Caffeinated beverages, particularly strong ones, have become immensely popular in social situations and need to be asked about. Television shows popularize sitting in coffeehouses for long periods of time drinking coffee. Multiple new beverages have entered the market place with increasing amounts of caffeine. Virtually none of the media associated with all of this mentions anything about caffeine toxicity. As a result, patients who become caffeine-toxic may not even realize it. They may need to be educated that the amount of caffeine they are ingesting simply to be social is making them feel uncomfortable.”

Medscape: Dual Diagnoses, New Perspectives

Thousands are in mental institutions because of caffeine

“Thousands are in mental institutions today because of no greater matter than that of the use of caffeine. Psychiatrists are now publishing articles indicating that there are numerous cases of depression and anxiety in mental institutions who need no other treatment than to be taken off caffeine. It would seem that with such a simple remedy available, many thousands of people could be returned to their full usefulness promptly.

“However, the use of caffeine is so traditional and firmly entrenched that it is almost impossible to remove caffeinated drinks from the diet of patients in the mental institutions. Soft drink machines, coffee dispensers, and the traditional coffee break are common pastimes in mental institutions, and with those who are mentally ill at home.”

Calvin Thrash, M.D., Author, Food Allergies Made Simple

35. British Journal of Addiction: 1 in 10 people caffeine-intoxicated

“Although infrequently diagnosed, caffeinism is thought to afflict as many as one person in ten of the population.”

JE James and KP Stirling, “Caffeine: A Summary of Some of the Known and Suspected Deleterious Habits of Habitual Use,”

36. Johns Hopkins University School of Medicine: Patients may fail to recognize caffeine-induced symptoms

“The potential for caffeine intoxication to cause clinically significant distress is reflected by the inclusion of caffeine intoxication as a diagnosis in DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition)(American Psychiatric Association, 1994) and in ICD-10 (International Statistical Classification of Diseases and Related Health Problems, Tenth Edition)(World Health Organization).”

“Studies have shown that high dietary doses of caffeine (200 mg or more) increase anxiety ratings and induce panic attacks in the general population. In the United States the average per capita daily intake among adult caffeine consumers is 280 milligrams (the equivalent of 17 ounces of brewed coffee).”

“Although highly anxious individuals tend to be more likely to limit their caffeine use, not all individuals with anxiety problems naturally avoid caffeine, and some may fail to recognize the role that caffeine is playing in their anxiety symptoms.”

“It has been noted that caffeine intoxication can occur in someone who has been using caffeine for many years with no prior apparent problems.”

Roland R. Griffiths, Ph.D, The Johns Hopkins University School of Medicine
Professor of Behavioral Biology, Department of Psychiatry & Behavioral Sciences
Professor of Neuroscience, Department of Neuroscience

37. Caffeinated persons are routinely “misdiagnosed as neurotic or even psychotic”

“In over a decade of practice as a clinical nutritionist, I have seen firsthand, with thousands of clients, that caffeine is a health hazard. Anxiety, muscle aches, PMS, headaches....However, if that’s all caffeine has done to you, you’re lucky. What about people misdiagnosed as neurotic or even psychotic, who spend years and small fortunes in psychotherapy—all because no one asked them about their caffeine intake?”

Nutritional biochemist Stephen Cherniske, in *Caffeine Blues: Wake Up to the Dangers of America’s #1 Drug*

38. Journal of the American Medical Association: Caffeine induces “psychological problems”

“The existence of a caffeine dependence syndrome, which includes evidence of continued caffeine consumption despite medical or psychological problems from caffeine consumption and unsuccessful efforts to quit caffeine use, provides a further similarity between caffeine and classic drugs of dependence.”

EC Strain, GK Mumford, K Silverman et al., “Caffeine Dependence Syndrome: Evidence from case histories and experimental evaluations.” *Journal of the American Medical Association*, 1995;273:1418-19.

39. “Psychosis can be induced in normal individuals ingesting caffeine at toxic doses.”

“Psychosis can be induced in normal individuals ingesting caffeine at toxic doses, and psychotic symptoms can also be worsened in schizophrenic patients using caffeine....Prevention of caffeine-induced psychiatric symptoms is possible by recognizing, educating, and treating patients using a tapering approach.”

Broderick P, Benjamin AB, Caffeine and psychiatric symptoms: A Review; *J Okla State Medical Assoc*, 2004 Dec; 97(12):538-42

40. Caffeine produces anxiety, psychotic states, toxic dementia

“An allergic reaction to caffeine manifests as anaphylaxis. During a state of caffeine anaphylaxis, the body enters the fight or flight mode, which may be mistaken as hyperactivity, anxiety, or panic disorder. Caffeine anaphylaxis causes cerebral vasculitis, leads to the breakdown of the blood brain barrier, and generates toxic dementia.”

“Symptoms range from minimal reactions to severe psychotic states, which may include irrational behavior, disruptions in attention, lack of focus and comprehension, mood changes, lack of organizational skills, abrupt shifting of activities, delusions, hallucinations, and paranoia.”

“An allergic reaction to caffeine results in poisoning of the prefrontal cortex. Damage to the underside area on the prefrontal cortex, above the eye sockets, generally renders a person absent minded and interferes with the ability to monitor personal activities (Carter, 1998). Injury results in loss of verbal and social inhibition....”

“While others may notice menacing changes in behavior or personality changes, the victim may not.”

Ruth Whalen, MLT

41. Data Sheet on caffeine exposure: Hallucinations, nervousness, psychosis

While the FDA labels caffeine as GRAS (“Generally Regarded As Safe”), chemical manufacturers are required by law to label caffeine “potentially fatal if inhaled, swallowed or absorbed through the skin” when handling and transporting it. Following is an excerpt from one Material Data Safety Sheet, courtesy of the University of California:

CAFFEINE: TOXIC.

ACUTE EXPOSURE- Ingestion of large amounts may result in headache, lightheadedness, dizziness, chills, fever, excitement, restlessness, nervousness, insomnia, mild delirium, hallucinations, tinnitus, constricted pupils, decreased visual fields, amblyopia, diplopia, photophobia, and scintillating scotoma. Neurologic symptoms may persist for several days....Other effects may include alternating states of consciousness and muscle twitching, tremors, hyperesthesia, hypertonicity or hypotonicity, trismus, opisthotonus and convulsions. Seizures generally precede death.

CHRONIC EXPOSURE- In addition to the effects detailed in acute exposure, agitation, disturbed sleep, caffeine-induced psychosis, heartburn and hyperventilation may occur. Prolonged use of high doses may result in tolerance, physical and psychological dependence. Symptoms of withdrawal may occur following abrupt cessation.

University of California Material Safety Data Sheet

42. Caffeine causes depression

“There is no doubt that the excitation of the central nervous system produced by large amounts of caffeine is followed by depression.”

J. Murdoch Ritchie, Professor Emeritus, Department of Pharmacology, Yale University School of Medicine, in *The Pharmacological Basis of Therapeutics*, Goodman and Gilman eds.

43. Biochemist finds 50% of anxiety cases caffeine-induced

“If a person were injected with 500 milligrams of caffeine [less than the dosage recently discovered in some 16-ounce Starbucks brews], within about an hour he or she would exhibit symptoms of severe mental illness, among them hallucinations, paranoia, panic, mania, and depression. But the same amount of caffeine administered over the course of a day only produces the milder forms of insanity for which we take tranquilizers and antidepressants.”

“For five years I worked in a team practice with physicians and psychotherapists. Often, the psychological evaluation would include one or more anxiety syndromes, and the recommendation was for counseling. I would point out that the person was consuming excessive amounts of caffeine and request a trial month off caffeine prior to therapy sessions. In about 50% of cases, the anxiety syndrome would resolve with caffeine withdrawal alone.”

Nutritional biochemist Stephen Cherniske, Author, Caffeine Blues: Wake Up to the Dangers of America’s #1 Drug

44. “Too many clinical histories fail to record caffeine use.”

“Diagnosis of any caffeine-related disorder begins with clinical awareness. Beverage caffeine is such a common component of social activity that its consideration as a psychostimulant often is neglected.”

“Too many clinical histories fail to record caffeine use. A complete caffeine history includes doses associated with beverages and medications....The observable signs associated with caffeine consumption are dose dependent. For most individuals who consume caffeine in the average range, the physical stigmata will include arousal signs. Expect to see nervousness, elevated heart rate, increased respiratory rate, flushed face, and an exaggerated startle response. Caffeine is a mild diuretic and may contribute to vague gastrointestinal complaints. In rare cases where an individual’s dose exceeds 1 gram per day, the picture changes. Gross muscle tremors, highly disorganized speech, and possible arrhythmias herald a more sinister outcome.” [CaffeineWeb note: One gram has long been considered the toxic dose of caffeine, but it may not be as rare as supposed. A recent study published in the Journal of Analytical Toxicology found that two 16 oz. Starbucks coffees may contain in excess of one gram.]

R. Gregory Lande, DO, FACN, Deputy and Director of Professional Services, Department of Clinical Administration, William S. Hall Psychiatric Institute, University of South Carolina

45. The New England Journal of Medicine: Patient’s mania a result of caffeine intake

Psychiatrists’ initial verdict on one caffeine-poisoned patient, in a case cited by Dr. Edward M. Brecher in the landmark “Consumers Union Report on Licit and Illicit Drugs”:

“Hysteria without question. When she failed to improve and remained wildly

manic for several days, she was transferred to a psychiatric hospital, where she was at first kept tied to a bed. After almost two months in the hospital, during which she slowly recovered, a mild relapse occurred. Investigation showed that she was drinking coffee, four cups a day. At this point, suspicion for the first time turned to caffeine. Coffee and tea were removed from her vicinity and soon she again became entirely normal, and was dismissed from the hospital.”

“Caffeine Intoxication: Report of a Case the Symptoms of which Amounted to a Psychosis,” *New England Journal of Medicine*, 1936;215:616-620.

46. Journal of Affective Disorders: Woman’s bipolar disorder vanishes as caffeine intake is discontinued

“A longitudinal case report shows a sudden remission of the severe course of a seasonal bipolar disorder after 10 years of psychopharmacological treatments. The discontinuation of heavy caffeine intake appears to have contributed to the outcome.”

Abstract of: L Tondo and N Rudas, “The course of a seasonal bipolar disorder influenced by caffeine,”
Journal of Affective Disorders, 1991;22 (4):249-251

47. NASA’s Caffeine Findings

In 1995, NASA’s Dr. David Noever and his fellow researchers at the Marshall Space Flight Center studied the webs spun by common house spiders (*Araneus diadematus*) dosed with several drugs, including LSD, marijuana, benzedrine, chloral hydrate and caffeine. The more toxic the drug, the less organized the web the spider created.

The spider on marijuana drifted off before finishing the job. The spider on benzedrine, an upper, worked energetically but without much planning. The spider dosed with chloral hydrate, a sedative, soon fell asleep.

To the surprise of Dr. Noever et al, caffeine did the most damage of all the substances tested. The spider dosed with it proved incapable of creating even a single organized cell, and its web showed no sign of the “hub and spokes” pattern fundamental to conventional web design.

What does the web of a caffeinated spider (which can hardly be accustomed to the jolt of a morning latte) have to do with human behavior? Unlikely as it sounds, it may be the most vivid illustration of caffeine’s disorienting effect on caffeine-sensitive people, many of whom may be misdiagnosed as mentally ill:

“Caffeine-induced psychosis, whether it be delirium, manic depression, schizophrenia, or merely an anxiety syndrome, in most cases will be hard to differentiate from other organic or non-organic psychoses....The treatment for caffeine-induced psychosis is to withhold further caffeine.”

Clinical Management of Poisoning and Drug Overdose, 3rd ed., 1998
Michael W. Shannon, MD, MPH, Director, Lead and Toxicology Clinic, The Children’s Hospital; Associate Professor of Pediatrics, Harvard Medical School; Staff Toxicologist, Massachusetts Poison Control System;
Lester M. Haddad, MD, Clinical Professor in Family Medicine, Medical University of South Carolina;
Emergency Physician and Active Staff, Bon Secours St. Francis Xavier Hospital; James F. Winchester, MD,
Professor of Medicine, Division of Nephrology, Georgetown University Medical Center

REGARDING WATER FLUORIDATION

J Public Health Dent. 1999 Fall;59(4):252-8.

Overview of the history and current status of fluoride supplementation schedules.

Adair SM.

Source Department of Pediatric Dentistry, Medical College of Georgia, Augusta 30912-1210, USA.
sadair@mail.mcg.edu

Abstract

Clinical trials of dietary fluoride supplements began in the 1940s in an effort to bring the benefits of fluoride to those who did not receive it through their drinking water. Following the early success of these trials, the Council on Dental Therapeutics of the American Dental Association (ADA) published its first recommendations for fluoride supplementation in 1958. The American Academy of Pediatrics (AAP) followed with its own recommendations in 1972. During the 1970s a variety of alternative schedules appeared in the literature, most in reaction to the findings of unexpectedly high levels of enamel fluorosis in children being supplemented with the AAP schedule. In 1979 the ADA and AAP agreed on essentially identical schedules. During the 1980s, however, the prevalence of enamel fluorosis continued to increase, and fluoride supplements were found in some studies to be a risk factor for fluorosis. This finding prompted another round of dosage schedule recommendations in the early 1990s. This paper presents a history of fluoride dosage recommendations and reviews the recent proposals for reducing supplement dosage.

48. FEBS Lett. 1997 May 26;408(3):315-8.

Aluminum fluoride associates with the small guanine nucleotide binding proteins.

Ahmadian MR, Mittal R, Hall A, Wittinghofer A.

Source

Max-Planck-Institut für molekulare Physiologie, Dortmund, Germany.

Abstract

AIF4⁻ has long been known to associate with and activate the GDP-bound alpha subunits of heterotrimeric G-proteins. Recently the small guanine nucleotide binding protein Ras has also been shown to associate with AIF4⁻ in the presence of stoichiometric amounts of its GTPase activating protein (GAP). Here we present the isolation of a stable Ras x GDP- x AIF4⁻ x GAP ternary complex by gel filtration. In addition, we generalise the association of AIF4⁻ with the small GTP-binding proteins by demonstrating ternary complex formation for the Cdc42, Rap and Ran proteins in the presence of their respective GAP proteins.

49. Mutat Res. 1989 Jun;223(2):191-203.

Sodium fluoride-induced chromosome aberrations in different stages of the cell cycle: a proposed mechanism.

Aardema MJ, Gibson DP, LeBoeuf RA.

Source

Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, OH 45239.

Erratum in Mutat Res 1989 Aug;223(4):417.

Abstract

In an attempt to clarify the controversy about sodium fluoride (NaF) clastogenicity, the induction of chromosome aberrations in Chinese hamster ovary cells (CHO) by NaF was investigated. Following a protocol used for screening chemicals for clastogenic activity, significant increases of aberrant cells were observed when cells were exposed to NaF for 4 h and harvested 8 h later. Cell-cycle kinetic studies demonstrated most cells were exposed in G2 of the cell cycle. Smaller increases in aberrant cells were observed when cells were harvested 20 h later (most cells were exposed in G1/S). The sensitivity of G2 cells to NaF was investigated further, along with the induction of aberrations at low doses. The results indicated that G2 cells are sensitive to NaF and the percent of aberrant cells increased with dose and length of exposure. With a 3-h exposure until harvest, no statistically significant increase in aberrant cells was observed at doses below 10 micrograms/ml NaF. These data are consistent with a threshold for NaF-induced clastogenicity around 10 micrograms/ml, as has been proposed previously (Scott and Roberts, 1987). It thus may be predicted that clastogenic effects would not occur in humans exposed to the levels of fluoride that are present in drinking water or dentifrices. An understanding of the mechanism of NaF-induced clastogenicity would help to clarify this point. It has previously been reported that NaF inhibits DNA synthesis/repair. The types of aberrations, mostly deletions and gaps, the induction of endoreduplicated cells, the cell-cycle delay and the sensitivity of G2 cells to NaF observed are similar to that reported in the literature for DNA synthesis/repair inhibitors like aphidicolin (APC). Similarities in the induction of aberrations by NaF and APC were confirmed in experiments with G2 cells. Based on these results and those previously reported for NaF and APC, it is proposed that NaF-induced aberrations may occur by an indirect mechanism involving the inhibition of DNA synthesis/repair.

50. Clin Dent. 1995;6(1):117-9.

**Serendipitous results of a pilot study: precaution indicated.
Heifetz SB, Proskin HM.**

Source

Dental Medicine and Public Health, School of Dentistry, University of Southern California, Los Angeles, USA.

Abstract

A pilot study was conducted to estimate sample size for a clinical trial in a F area. In 1992, 98 children 14 years of age living in Fall River, MA were examined for dental caries: Fall River was fluoridated in 1973. Residence histories showed that 74% lived there from birth (B), 12% were residents from kindergarten or 1st grade (K1) and 14% moved into the community at a later time (LT). Findings on caries prevalence showed an inverse relation between DMFS and initial age of residence; mean DMFS was 3.00 for Group B, 5.33 for Group K1 and 6.93 for Group LT. A one-way ANOVA indicated significant differences among the groups ($p=0.05$). Because residence from birth or from early life can be considered a proxy for systemic fluoride exposure, and because controversy currently surrounds the issue of topical versus systemic benefits in explaining the mechanism of action of fluoride, the results appeared to have importance. However, internal analyses of the data comparing surface-specific (pit and fissure) results among the groups for early erupting teeth with varying systemic exposure to fluoridated water and for late erupting teeth, all with appreciable systemic exposure, showed comparable relative differences in DMFS scores. Lack of internal validity, therefore, discounted a conclusion from overall results of the role of systemic fluorides in providing decay preventive benefits. If there is any conclusion that can be drawn it is that serendipitous escapades with data from a pilot study, if not rigorously analyzed and cautiously interpreted, tend to further muddy the waters (fluoridated in this case) on controversial issues and should best be avoided.

51. Exposure to high fluoride concentrations in drinking water is

associated with decreased birth rates

Journal of Toxicology and Environmental Health, Part A: Current Issues

Volume 42, Issue 1, 1994, Pages 109 - 121

Author: Stan C. Frenia

DOI: 10.1080/15287399409531866

Abstract

A review of fluoride toxicity showed decreased fertility in most animal species studied. The current study was to see whether fluoride would also affect human birth rates. A U.S. database of drinking water systems was used to identify index counties with water systems reporting fluoride levels of at least 3 ppm. These and adjacent counties were grouped in 30 regions spread over 9 states. For each county, two conceptionally different exposure measures were defined, and the annual total fertility rate (TFR) for women in the age range 10-49 yr was calculated for the period 1970-1988. For each region separately, the annual TFR was regressed on the fluoride measure and sociodemographic covariables. Most regions showed an association of decreasing TFR with increasing fluoride levels. Meta-analysis of the region-specific results confirmed that the combined result was a negative TFR/fluoride association with a consensus combined p value of .0002-.0004, depending on the analytical scenario. There is no evidence that this outcome resulted from selection bias, inaccurate data, or improper analytical methods. However, the study is one that used population means rather than data on individual women. Whether or not the fluoride effect on the fertility rate found at the county level also applies to individual women remains to be investigated.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TC0-475CJ7N-BH&_user=10&_coverDate=04%2F30%2F1994&_rdoc=1&_fmt=high&_orig=gateway&_origin=gateway&_sort=d&_docanchor=&_view=c&_searchStrId=1743251174&_rerunOrigin=scholar.google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=08668a2d8d9c3a416a14614187da5000&searchtype=a

52. Reproductive Toxicology

Volume 8, Issue 2, March-April 1994, Pages 155-159

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Original contribution

In vitro fluoride toxicity in human spermatozoa

Niloufer J. Chinoy, a and Murakonda V. Narayanaa

aReproductive Endocrinology & Toxicology Unit, Department of Zoology, School of Sciences, Gujarat University, Ahmedabad, India

Available online 6 November 2002.

Abstract

Effects of sodium fluoride (NaF) on washed, ejaculated human spermatozoa at doses of 25, 50, and 250 mM were investigated in vitro at intervals of 5, 10, and 20 min. Sodium fluoride (NaF) did not affect the extracellular pH of sperm, except that a slight acidification was caused by the 250 mM dose only. The treatment caused a significant enhancement in acid phosphatase (ACPase) and hyaluronidase activities after 5 and 10 min. However, the decrease in the lysosomal enzyme activity after 20 min treatment could have been due to the gradual increase in fluoride accumulation by spermatozoa leading to membrane damage. Silver nitrate staining of sperm revealed elongated heads, deflagellation, and loss of the acrosome together with coiling of the tail. Sperm glutathione levels also showed a time-dependent decrease with complete depletion after 20 min indicating rapid glutathione oxidation in detoxification of the NaF. The altered lysosomal enzyme activity and glutathione levels together with morphologic anomalies resulted in a significant decline in sperm motility with an effective dose of 250 mM.

53. Serum Parathyroid Hormone Levels in Chronic Endemic Fluorosis

Banu Kale Koroglu, Ismail Hakki Ersoy, Mert Koroglu, Ayşe Balkarli, Siddika Ersoy, Simge Varol and Mehmet Numan Tamer

Abstract

Endemic waterborne fluorosis is a public health problem in Isparta, a city located in southern Turkey. Fluoride is a cumulative element that increases metabolic turnover of the bone and also affects the homeostasis of bone mineral metabolism. There are number of similarities between the effects of excess parathyroid hormone (PTH) and fluorosis on bone. So fluoride might show its effect via PTH. We aimed to determine PTH levels in patients with endemic fluorosis to estimate the possible toxic effects of chronic fluoride intake. Fifty-six patients with endemic fluorosis and 28 age-, sex-, and body-mass-index-matched healthy controls were included in this study. Endemic fluorosis was diagnosed according to the clinical diagnosis criteria of Wang. The urine fluoride levels of fluorosis patients were significantly higher than those of control subjects as expected (1.9 ± 0.1 vs. 0.4 ± 0.1 mg/L, respectively; $P < 0.001$). PTH levels in fluorosis group were significantly higher than control group (65.09 ± 32.91 versus 47.40 ± 20.37 , respectively; $P = 0.01$). The results of our study demonstrate that serum PTH levels are increased in patients with endemic fluorosis. Fluoride, by interfering calcium balance, may be the cause of secondary hyperparathyroidism.

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54. Indian Journal of Pediatrics

Volume 65, Number 3, 371-381, DOI: 10.1007/BF02761130

Symposium: Toxicology and Poisoning—II

Endemic chronic fluoride toxicity and dietary calcium deficiency interaction syndromes of metabolic bone disease and deformities in India: Year 2000

Abstract

Epidemiological studies during 1963–1997 were conducted in 45,725 children exposed to high intake of endemic fluoride in the drinking water since their birth. Children with adequate (dietary calcium >800 mg/d) and inadequate (dietary calcium <300 mg/d) calcium nutrition and with comparable intakes of fluoride (mean 9.5 ± 1.9 mg/d) were compared. The toxic effects of fluoride were severe and more complex and the incidence of metabolic bone disease (rickets, osteoporosis, PTH bone disease) and bony leg deformities (genu valgum, genu varum, bowing, rotational and wind-swept) was greater ($>90\%$) in children with calcium deficiency as compared to $<25\%$ in children with adequate calcium who largely had osteosclerotic form of skeletal fluorosis with minimal secondary hyperparathyroidism.

The syndrome of skeletal fluorosis and associated metabolic bone disease and deformity is a unique clinical entity classified as a variant of osteosclerotic form of skeletal fluorosis. This syndrome chiefly results from the biological impact of excess fluoride, low calcium, high PTH and $1,25(\text{OH})_2\text{D}_3$ separately and through their interactions on bone structure and metabolism as studied by radiology, bone scanning, bone histomorphometry and relevant metabolic and endocrine laboratory investigations. Metabolically active and vascular bones of children accumulate fluoride at faster and greater rate than adults (at the sites of active growth). In calcium deficient children the toxic effects of fluoride manifest even at marginally high (> 2.5 mg/d) exposures to fluoride. Fluoride toxicity also exaggerates the metabolic effects of calcium deficiency on bone. The findings strongly suggest that children with calcium deficiency rickets reported in the literature should be re-investigated for possible fluoride interactions. Deep bore drinking water supply with fluoride <0.5 ppm and improvement of calcium nutrition provide 100% protection against the toxic effects of fluoride and are recommended as the cost effective

and practical public health measures for the prevention and control of endemic fluorosis.

55. Excerpt from:

Adams PH, Jowsey J. (1965). Sodium Fluoride in the Treatment of Osteoporosis and Other Bone Diseases. Annals of Internal Medicine. 63(6): 1151-1155. pg. 1154:

"In some animals sodium fluoride causes severe renal damage; renal tubular damage and renal insufficiency have been reported in endemic fluorosis (16). These renal effects of fluorine may be important, particularly when long-term therapy is contemplated. The presence of pre-existing renal disease may also influence the response to the drug, because the kidney is the principal route of fluorine excretion. A patient with renal disease (probably chronic pyelonephritis) has been reported (17) whose bone contained fluorine in a concentration exceeding 5,000 ppm. There was no history of exposures to fluorides, and her usual drinking water contained less than 0.5 ppm of fluorine. This is of interest because in a postmortem study in Utah (18) the highest concentrations of fluorine were found in those with chronic pyelonephritis; this was not true of those with chronic glomerulonephritis. It is hard to explain these findings but in chronic pyelonephritis there is commonly a defect of water conservation with polyuria and polydipsia, and this may be the important factor. Sauerbrunn and associates have reported in this issue of the ANNALS the development of skeletal fluorosis in a patient with chronic polydipsia; the fluorine content of his drinking water was high but it was not at a level generally associated with the production of skeletal disorder. It seems probable that in this patient and in those with chronic pyelonephritis the high concentrations of fluorine found in the bone are the result of a greater consumption of water, which leads to a greater intake of fluorine."

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 17. Taves, D.R., Terry, R., Smith, F.A., Gardner, D.E.: Use of fluoridated water in long-term hemodialysis. *Arch. Intern. Med. (Chicago)* 115: 167, 1965.
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56. Zhonghua Bing Li Xue Za Zhi. 1992 Aug;21(4):218-20.

The effect of fluorine on the developing human brain

[Article in Chinese]

Du L.

Source Department of Pathology, Guiyang Medical College.

Abstract

Fifteen therapeutically aborted fetuses at the 5th-8th gestation month from the endemic fluorosis area were compared with those from the non-endemic area. Stereological study of the brains showed that the numerical density of volume of the neurons and the undifferentiated neuroblasts as well as the nucleus-cytoplasm ratio of the neurons were increased. The mean volume of the neurons was reduced. The numerical density of volume, the volume density and the surface density of the mitochondria were significantly reduced. The results showed that chronic fluorosis in the course of intrauterine fetal life may produce certain harmful effects on the developing brain of the fetus.

57. Toxicology. 2003 Feb 1;183(1-3):235-42.

Selective decreases of nicotinic acetylcholine receptors in PC12 cells exposed to fluoride.

Chen J, Shan KR, Long YG, Wang YN, Nordberg A, Guan ZZ.

Source Department of Pathology, Guiyang Medical College, Guiyang 550004, Guizhou, PR China.

Abstract

In an attempt to elucidate the mechanism by which excessive fluoride damages the central nervous system, the effects of exposure of PC12 cells to different concentrations of fluoride for 48 h on nicotinic acetylcholine receptors (nAChRs) were characterized here. Significant reductions in the number of binding sites for both [3H] epibatidine and [125I]alpha-bungarotoxin, as well as a significant decrease in the B(max) value for the high-affinity of epibatidine binding site were observed in PC12 cells subjected to high levels of fluoride. On the protein level, the alpha 3 and alpha 7 subunits of nAChRs were also significantly decreased in the cells exposed to high concentrations of fluoride. In contrast, such exposure had no significant effect on the level of the beta 2 subunit. These findings suggest that selective decreases in the number of nAChRs may play an important role in the mechanism(s) by which fluoride causes dysfunction of the central nervous system.

58. Indian J Exp Biol. 2002 May;40(5):546-54.

Neurotoxicity of fluoride: neurodegeneration in hippocampus of female mice.

Bhatnagar M, Rao P, Sushma J, Bhatnagar R.

Source

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Abstract

Light microscopic study of hippocampal sub-regions demonstrated significant number of degenerated nerve cell bodies in the CA3, CA4 and dentate gyrus(Dg) areas of sodium fluoride administered adult female mice. Ultrastructural studies revealed neurodegenerative characteristics like involution of cell membranes, swelling of mitochondria, clumping of chromatin material etc, can be observed in cell bodies of CA3, CA4 and dentate gyrus (Dg). Fluoride intoxicated animals also performed poorly in motor co-ordination tests and maze tests. Inability to perform well increased with higher fluoride concentration in drinking water.

59. Zhonghua Yu Fang Yi Xue Za Zhi. 2002 Jul;36(4):222-4.

[Studies on DNA damage and apoptosis in rat brain induced by fluoride].

[Article in Chinese]

Chen J, Chen X, Yang K, Xia T, Xie H.

Source Department of Environmental Health, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China.

Abstract

OBJECTIVE:

To explore the DNA damage effects and apoptosis in brain cells of rats induced by sodium fluoride.

METHODS:

SD rats were divided into two groups, i.e. control group and fluoride treated group, which were injected intraperitoneally with distilled water and sodium fluoride (20 mg.kg(-1).d(-1)) respectively. On the hand, 5 mmol/L NaF were used in in vitro study. Single Cell Gel Electrophoresis (SCGE or Comet Assay) was utilized to measure DNA damage and apoptosis was detected by the TUNEL method and Flow Cytometry (FCM).

RESULTS:

The DNA damage in pallium neurons in rats of the fluoride group was much more serious compared with those of the control group, with the Rdit value being 0.351 and 0.639 respectively ($P < 0.01$) in vivo, and 0.384 4 and 0.650 1 respectively ($P < 0.01$) in vitro. TUNEL positive cells were found in pallium, hippocampus and cerebellar granule cells in rats of fluoride group, whereas those in the control group were rare. It was demonstrated by FCM results that the percentages of apoptotic cells both in pallium and hippocampus were significantly higher ($P < 0.01$) in rats of fluoride group (27.12 +/- 3.08, 34.97 +/- 5.46) than those in control group (4.63 +/- 0.98, 5.35 +/- 0.79), ($P < 0.01$).

CONCLUSION:

Sodium fluoride could induce DNA damage and apoptosis in rats brain.

60. Neurotoxicol Teratol. 2002 Nov-Dec;24(6):751-7.

Chronic fluoride toxicity decreases the number of nicotinic acetylcholine receptors in rat brain.

Long YG, Wang YN, Chen J, Jiang SF, Nordberg A, Guan ZZ.

Source Department of Pathology, Guiyang Medical College, Guizhou, PR China.

Abstract

In order to investigate the molecular mechanism(s) underlying brain dysfunction caused by chronic fluorosis, neuronal nicotinic acetylcholine receptors (nAChRs) in the brain of rats receiving either 30 or 100 ppm fluoride in their drinking water for 7 months were analyzed in the present study employing ligand binding and Western blotting. There was a significant reduction in the number of [3H]epibatidine binding sites in the brain of rats exposed 100 ppm of fluoride, but no alteration after exposed to 30 ppm. On the other hand, the number of [125I] alpha-BTX binding sites was significantly decreased in the brains of rats exposed to both levels of fluoride. Western blotting revealed that the level of the nAChR alpha4 subunit protein in the brains of rats was significantly lowered by exposure to 100 ppm, but not 30 ppm fluoride; whereas the expression of the alpha7 subunit protein was significantly decreased by both levels of exposure. In contrast, there was no significant change in the level of the beta2 subunit protein in the brains of rats administered fluoride. Since nAChRs play major roles in cognitive processes such as learning and memory, the decrease in the number of nAChRs caused by fluoride toxicity may be an important factor in the mechanism of brain dysfunction in the disorder.

61. Fluoride 2000; 33(1): 17-26

Effects of fluoride accumulation on some enzymes of brain and gastrocnemius muscle of mice

M Lakshmi Vani, K Pratap Reddy

Neurobiology Laboratory, Department of Zoology, Osmania University, Hyderabad - 500 007, Andhra Pradesh, India.

SUMMARY: This study reports accumulation of fluoride and altered activities of some enzymes involved in free-radical metabolism and membrane function in whole brain and gastrocnemius muscle of female mice treated with NaF (20mg/kg/body weight) for 14 days. The body weight and somatic index were decreased, whereas fluoride levels were significantly increased ($p < 0.01$) in both brain and gastrocnemius muscle. The enzymes SOD, GST, and catalase decreased significantly ($p < 0.01$) in contrast to XOD activity, which moderately increased. SDH, LDH, AIAT, AAT, and CPK activities and membrane-bound enzymes, viz $\text{Na}^+ - \text{K}^+$, Mg^{++} and Ca^{++} ATPase and AChE were decreased significantly ($p < 0.01$) in both brain and gastrocnemius muscle. The effect of fluoride on enzymes of muscle was comparatively larger, which corroborates the greater accumulation of fluoride in muscle than brain. This study therefore shows that both brain and muscle are affected by fluoride with inhibition of some enzymes associated with free-radical metabolism, energy production and transfer, membrane transport, and synaptic transmission, but with an enhanced activity of XOD.

62. Toxicology. 2004 Aug 5;200(2-3):169-77.

Decreased nicotinic receptors in PC12 cells and rat brains influenced by fluoride toxicity--a mechanism relating to a damage at the level in post-transcription of the receptor genes.

Shan KR, Qi XL, Long YG, Nordberg A, Guan ZZ.

Source Department of Molecular Biology, Guiyang Medical College, 550004, Guizhou, PR China.

Abstract

In order to reveal mechanisms of the decreased nicotinic acetylcholine receptors (nAChRs) resulted from fluoride toxicity, we treated PC12 cells by different concentrations of fluoride (0.1-100 ppm) for 48 h, and exposed rats to high doses of fluoride (30 and 100 ppm) in their drinking water for 7 months. The expression of nAChRs at mRNA and protein levels, neurotoxicity and oxidative stress were analyzed in the study. The results indicated that there were no significant changes at mRNA level of the nAChR alpha3, alpha7, beta2 subunits in PC12 cells, and alpha4, alpha7, beta2 subunits in rat brains between the groups with fluorosis and controls. A significant decline in 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction, and increased levels of protein oxidation and lipid peroxidation were observed in PC12 cells treated with high doses of fluoride or rat brains with chronic fluorosis. The decreases of nAChR alpha3 and alpha7 subunit proteins in PC12 cells resulted from fluoride toxicity were mostly prevented by a pretreatment with antioxidant. The results suggest that the deficit of nAChRs induced by fluoride toxicity occurs at the level of post-transcription of the receptor gene, in which a mechanism might be involved in the damage by oxidative stress.

63. Brain Res. 1998 Feb 16;784(1-2):284-98.

Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water: alterations in neuronal and cerebrovascular integrity.

Varner JA, Jensen KF, Horvath W, Isaacson RL.

Source Psychology Department, Binghamton University, Binghamton, NY, USA.

Abstract

This study describes alterations in the nervous system resulting from chronic administration of the fluoroaluminum complex (AlF₃) or equivalent levels of fluoride (F) in the form of sodium-fluoride (NaF). Twenty seven adult male Long-Evans rats were administered one of three treatments for 52 weeks: the control group was administered double distilled deionized drinking water (ddw). The aluminum-treated group received ddw with 0.5 ppm AlF₃ and the NaF group received ddw with 2.1 ppm NaF containing the equivalent amount of F as in the AlF₃ ddw. Tissue aluminum (Al) levels of brain, liver and kidney were assessed with the Direct Current Plasma (DCP) technique and its distribution assessed with Morin histochemistry. Histological sections of brain were stained with hematoxylin & eosin (H&E), Cresyl violet, Bielschowsky silver stain, or immunohistochemically for

beta-amyloid, amyloid A, and IgM. No differences were found between the body weights of rats in the different treatment groups although more rats died in the AIF3 group than in the control group. The AI levels in samples of brain and kidney were higher in both the AIF3 and NaF groups relative to controls. The effects of the two treatments on cerebrovascular and neuronal integrity were qualitatively and quantitatively different. These alterations were greater in animals in the AIF3 group than in the NaF group and greater in the NaF group than in controls.

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64. The Effect of Fluoride on the Physiology of the Pineal Gland

Luke J.

Ph.D Dissertation, School of Biological Sciences, University of Surrey, UK. 1997.

The purpose was to discover whether fluoride (F) accumulates in the pineal gland and thereby affects pineal physiology during early development. The [F] of 11 aged human pineals and corresponding muscle were determined using the F-electrode following HMDS/acid diffusion. The mean [F] of pineal gland was significantly higher ($p < 0.001$) than muscle: 296 ± 257 vs 0.5 ± 0.4 mg/kg respectively. Secondly, a controlled longitudinal experimental study was carried out to discover whether F affects the biosynthesis of melatonin, (MT), during pubertal development using the excretion rate of urinary 6-sulphatoxymelatonin, (aMT6s), as the index of pineal MT synthesis. Urine was collected at 3-hourly intervals over 48 hours from two groups of gerbils, (*Meriones unguiculatus*), low-F (LF) and high-F (HF) (12 f, 12 m/group): under LD: 12 12, from prepubescence to reproductive maturity (at 9-12 weeks) to adulthood, i.e., at 7, 9, 11 1/2 and 16 weeks. The HF pups received 2.3 ug F/g BW/day from birth until 24 days whereafter HF and LF groups received food containing 37 and 7 mg F/kg respectively and distilled water. Urinary aMT6s levels were measured by radioimmunoassay. The HF group excreted significantly less aMT6s than the LF group until the age of sexual maturation. At 11 1/2 weeks, the circadian profile of aMT6s by the HF males was significantly diminished but, by 16 weeks, was equivalent to the LF males. In conclusion, F inhibits pineal MT synthesis in gerbils up until the time of sexual maturation. Finally, F was associated with a significant acceleration of pubertal development in female gerbils using body weights, age of vaginal opening and accelerated development of the ventral gland. At 16 weeks, the mean testes weight of HF males was significantly less ($p < 0.002$) than that of the LF males. The results suggest that F is associated with low circulating levels of MT and this leads to an accelerated sexual maturation in female gerbils. The results strengthen the hypothesis that the pineal has a role in pubertal development.

65. Caries Res. 2001 Mar-Apr;35(2):125-8.

Fluoride deposition in the aged human pineal gland.

Luke J.

**Source School of Biological Sciences, University of Surrey,
Guildford, UK. jenniluke@compuserve.com**

Abstract

The purpose was to discover whether fluoride (F) accumulates in the aged human pineal gland. The aims were to determine (a) F-concentrations of the pineal gland (wet), corresponding muscle (wet) and bone (ash); (b) calcium-concentration of the pineal. Pineal, muscle and bone were dissected from 11 aged cadavers and assayed for F using the HMDS-facilitated diffusion, F-ion-specific electrode method. Pineal calcium was determined using atomic absorption spectroscopy. Pineal and muscle contained 297 ± 257 and 0.5 ± 0.4 mg F/kg wet weight, respectively; bone contained $2,037 \pm 1,095$ mg F/kg ash weight. The pineal contained $16,000 \pm 11,070$ mg Ca/kg wet weight. There was a positive correlation between pineal F and pineal Ca ($r = 0.73$, $p < 0.02$) but no correlation between pineal F and bone F. By old age, the pineal gland has readily accumulated F and its F/Ca ratio is higher than bone.

When Dr.Null asserts that ".....Phosphatidyl Serine, herbs, amino acids, anti-oxidants and B-vitamins can help achieve optimal brain function....", Dr. Barrett asks: [How has he (*Dr. Null - italics mine*) determined that *this* can help people improve brain function?]

66. REGARDING PHOSPHATIDYL SERINE

<http://www.ncbi.nlm.nih.gov/pubmed/8323999>

Cognitive decline in the elderly: a double-blind, placebo-controlled multicenter study on efficacy of phosphatidylserine administration.

Cenacchi T, Bertoldin T, Farina C, Fiori MG, Crepaldi G.
Source
Aging (Milano). 1993 Apr;5(2):123-33.

Fidia Research Laboratories, Abano Terme (Padova), Italy.

Abstract

This double-blind study assesses the therapeutic efficacy and the safety of oral treatment with phosphatidylserine (BC-PS) vs placebo (300 mg/day for 6 months) in a group of geriatric patients with cognitive impairment. A total of 494 elderly patients (age between 65 and 93 years), with moderate to severe cognitive decline, according to the Mini Mental State Examination and Global Deterioration Scale, were recruited in 23 Geriatric or General Medicine Units in Northeastern Italy. Sixty-nine patients dropped out within the 6-month trial period. Patients were examined just before starting therapy, and 3 and 6 months thereafter. The efficacy of treatment compared to placebo was measured on the basis of changes occurring in behavior and cognitive performance using the Plutchik Geriatric Rating Scale and the Buschke Selective Reminding Test. Statistically significant improvements in the phosphatidylserine-treated group compared to placebo were observed both in terms of behavioral and cognitive parameters. In addition, clinical evaluation and laboratory tests demonstrated that BC-PS was well tolerated. These results are clinically important since the patients were representative of the geriatric population commonly met in clinical practice.

<http://www.ncbi.nlm.nih.gov/pubmed/21103402>

Clin Interv Aging. 2010 Nov 2;5:313-6.

67. The effect of phosphatidylserine-containing omega-3 fatty acids on memory abilities in subjects with subjective memory complaints: a pilot study.

Richter Y, Herzog Y, Cohen T, Steinhart Y.
Source Enzymotec LTD, Migdal-HaEmeq, Israel.

Abstract

OBJECTIVE:

To evaluate for the first time the efficacy of safe-sourced phosphatidylserine-containing omega-3 long chain polyunsaturated fatty acid (PS-omega-3) in improving memory abilities.

METHODS:

PS-omega-3 was administered daily for 6 weeks to eight elderly volunteers with subjective memory complaints. The Cognitive Drug Research test battery was used to assess the effect on their cognitive abilities.

RESULTS:

PS-omega-3 supplementation resulted in 42% increase in the ability to recall words in the delayed condition.

CONCLUSION:

PS-omega-3 may have a favorable effect on memory in subjects with subjective memory complaints. PS-omega-3 may serve as a safe alternative to phosphatidylserine extracted from bovine cortex.
PMID: 21103402 [PubMed - indexed for MEDLINE] PMCID: PMC2981104

<http://onlinelibrary.wiley.com/doi/10.1111/j.1600-0447.1990.tb06494.x/abstract>

68. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders

M. Maggioni¹, G.B. Picotti², G.P. Bondiolotti³, A. Panerai³, T. Cenacchi⁴, P. Nobile⁵, F. Brambilla^{5,*}

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Issue

Acta Psychiatrica Scandinavica

Volume 81, Issue 3, pages 265–270, March 1990

Keywords:

aging;depression;phosphatidylserine;adrenoceptor;noradrenaline;amine metabolite

The effects of phosphatidylserine (BC-PS) on cognitive, affective and behavioural symptoms were studied in a group of 10 elderly women with depressive disorders. Patients were treated with placebo for 15 days, followed by BC-PS (300 mg/day) for 30 days. The Hamilton Rating Scale for Depression, Gottfries-Bråne-Steen Rating Scale, Nurse's Observation Scale for Inpatient

Evaluation and Buschke Selective Reminding Test were administered before and after placebo and after BC-PS therapy, to monitor changes in depression, memory and general behaviour. At the same time, basal plasma levels of noradrenaline, MHPG, DOPAC, HVA and 5-HIAA, and GH/ β -endorphin/ β -lipotropin responses to clonidine stimulation were measured. BC-PS induced consistent improvement of depressive symptoms, memory and behaviour. No changes in amine metabolite levels or in hormonal responses to α 2-adrenoceptor stimulation were observed.

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10. Hershowitz M, et al. Long-term treatment of dementia Alzheimer type with

phosphatidylserine: effect on cognitive functioning and performance in daily life. In, Bazan NG, et al (eds) *Phospholipids in the Nervous System: Biochemical and Molecular Pathology*, 1989. Padua, Italy: Liviana Press.

11. Maggioni, M, Picotti, G.B., Bondiolotti, G.P., Panerai, A. Cenacchi, T. Nobil, P. and Brambilla, F. Effects of phosphatidylserine therapy in geriatric patients with depressive disorders. *Acta Psychiatr. Scand.* 1990. 81: 265-70.

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16. Ransmayr, G, Plover, S, Gerstenbrand, F, and Bauer, G. Double-blind placebo-controlled trial of phosphatidylserine in elderly patients with arteriosclerotic encephalopathy. *Clin. Trials J.*, 1987. 24: 62-72.

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<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0012244>

69. Homocysteine-Lowering by B Vitamins Slows the Rate of Accelerated Brain Atrophy in Mild Cognitive Impairment: A Randomized Controlled Trial

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Abstract

Background

An increased rate of brain atrophy is often observed in older subjects, in particular those who suffer from cognitive decline. Homocysteine is a risk factor for brain atrophy, cognitive impairment and dementia. Plasma concentrations of homocysteine can be lowered by dietary administration of B vitamins.

Objective

To determine whether supplementation with B vitamins that lower levels of plasma total homocysteine can slow the rate of brain atrophy in subjects with mild cognitive impairment in a randomised controlled trial (VITACOG, ISRCTN 94410159).

Methods and Findings

Single-center, randomized, double-blind controlled trial of high-dose folic acid, vitamins B6 and B12 in 271 individuals (of 646 screened) over 70 y old with mild cognitive impairment. A subset (187) volunteered to have cranial MRI scans at the start and finish of the study. Participants were randomly assigned to two groups of equal size, one treated with folic acid (0.8 mg/d), vitamin B12 (0.5 mg/d) and vitamin B6 (20 mg/d), the other with placebo; treatment was for 24 months. The main outcome measure was the change in the rate of atrophy of the whole brain assessed by serial volumetric MRI scans.

Results

A total of 168 participants (85 in active treatment group; 83 receiving placebo) completed the MRI section of the trial. The mean rate of brain atrophy per year was 0.76% [95% CI, 0.63–0.90] in the active treatment group and 1.08% [0.94–1.22] in the placebo group ($P = 0.001$). The treatment response was related to baseline homocysteine levels: the rate of atrophy in participants with homocysteine $>13 \mu\text{mol/L}$ was 53% lower in the active treatment group ($P = 0.001$). A greater rate of atrophy was associated with a lower final cognitive test scores. There was no difference in serious adverse events according to treatment category.

Conclusions and Significance

The accelerated rate of brain atrophy in elderly with mild cognitive impairment can be slowed by treatment with homocysteine-lowering B vitamins. Sixteen percent of those over 70 y old have mild cognitive impairment and half of these develop Alzheimer's disease. Since accelerated brain atrophy is a characteristic of subjects with mild cognitive impairment who convert to Alzheimer's disease, trials are needed to see if the same treatment will delay the development of Alzheimer's disease.

Trial Registration

Controlled-Trials.com ISRCTN94410159

[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(07\)60109-3/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)60109-3/fulltext)

**70. The Lancet, Volume 369, Issue 9557, Pages 208 - 216,
20 January 2007**

doi:10.1016/S0140-6736(07)60109-3

Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial

Dr Jane Durga PhD a b , Martin PJ van Boxtel PhD c, Prof Evert G Schouten PhD a, Prof Frans J Kok PhD a, Prof Jelle Jolles PhD c, Martijn B Katan PhD b, Petra Verhoef PhD a b

Summary

Background

Low folate and raised homocysteine concentrations in blood are associated with poor cognitive performance in the general population. As part of the FACIT trial to assess the effect of folic acid on markers of atherosclerosis in men and women aged 50—70 years with raised plasma total homocysteine and normal serum vitamin B12 at screening, we report here the findings for the secondary endpoint: the effect of folic acid supplementation on cognitive performance.

Methods

Our randomised, double blind, placebo controlled study took place between November, 1999, and December, 2004, in the Netherlands. We randomly assigned 818 participants 800 µg daily oral folic acid or placebo for 3 years. The effect on cognitive performance was measured as the difference between the two groups in the 3-year change in performance for memory, sensorimotor speed, complex speed, information processing speed, and word fluency. Analysis was by intention-to-treat. This trial is registered with clinicaltrials.gov with trial number NCT00110604.

Findings

Serum folate concentrations increased by 576% (95% CI 539 to 614) and plasma total homocysteine concentrations decreased by 26% (24 to 28) in participants taking folic acid compared with those taking placebo. The 3-year change in memory (difference in Z scores 0·132, 95% CI 0·032 to 0·233), information processing speed (0·087, 0·016 to 0·158) and sensorimotor speed (0·064, -0·001 to 0·129) were significantly better in the folic acid group than in the placebo group.

Interpretation

Folic acid supplementation for 3 years significantly improved domains of cognitive function that tend to decline with age. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial

71. Improvement in Cognition and Mood With Multivitamin/Mineral in Healthy Males

12/1/2010

Tina Kaczor, ND, FABNO

Cognitive and Mood improvements seen as soon as one month after beginning vitamin/mineral supplementation.

Wednesday, December 01, 2010

by: Tina Kaczor, ND, FABNO

Section: Abstracts & Commentary

Tina Kaczor, ND, FABNO, is a naturopathic physician, board certified in naturopathic oncology. She received her naturopathic doctorate from National College of Natural

Medicine, and completed her residency in naturopathic oncology at Cancer Treatment Centers of America in Tulsa, Okla. Dr. Kaczor received undergraduate degrees from the State University of New York at Buffalo. She is the current treasurer of the Oncology Association of Naturopathic Physicians and secretary of the American Board of Naturopathic Oncology. She is adjunct faculty at National College of Natural Medicine as well as the Helfgott Research Institute in Portland, Ore. She has been published in several peer-reviewed journals. For more information visit: Clinic of Natural Medicine

Reference

Kennedy D, Veasey R, Watson A, et al. Effects of high-dose B vitamin complex with vitamin C and minerals on subjective mood and performance in healthy males

Psychopharmacology. 2010;211:55-68.

Design

Randomized, placebo-controlled, double-blind trial

Participants

215 healthy male volunteers ages 30–55 were recruited. 210 completed the study (placebo group = 107, multivitamin/mineral group = 103).

Intervention

1 tablet daily of a multivitamin/mineral (Berocca®). Each tablet contained: B1 (15 mg), B2 (15 mg), B6 (10 mg), B12 (10 mcg), vitamin C (500 mg), biotin (150 mcg), folic acid (400 mcg), nicotinamide (50 mg) pantothenic acid (23 mg), calcium (100 mg), magnesium (100 mg), and zinc (10 mg).

Primary Outcome Measures

Cognitive assessment was done 1 day prior and 1 day following 33 days of intervention or placebo. A Profile of Mood States (POMS), Perceived Stress Scale (PSS), and the General Health Questionnaire-12 (GHQ-12) were used. A 60-minute cognitive demand battery was also performed at baseline and study conclusion.

Key Findings

The intervention group had significant improvements in the PSS, the GHQ-12 and the “vigour” subscale of the POMS questionnaire. In addition, the intervention group performed better on the serial 3 subtraction test and reported they were less “mentally tired” both before and after the cognitive testing at the study’s conclusion.

Clinical Implications

The use of vitamin/mineral supplementation in healthy adults is growing in popularity. Whether this is beneficial in populations assumed to be nutrient-replete and without

any pathology is not known. This study, while small, suggests that cognitive and mood improvements may be seen as soon as 1 month after beginning a B complex with vitamin C and calcium/magnesium/zinc.

As with any nutrient intervention study, the question of nutrient deficiency in participants prior to the intervention must be asked. This Swiss study is notable for its recruitment of healthy, fully employed males, a population presumed to be adequately nourished. While adequate nutrient status was assumed, no serum measurements were performed. Intake of fruits and vegetables was 3.71 servings on average in the intervention group. In a 2005 U.S. survey of fruit and vegetable consumption, only 27.2% of adults ate 3 or more servings of vegetables per day.¹ The significant improvement in cognitive ability and mood from the supplemental intervention in this trial implies that participants had suboptimal levels of one or more of the nutrients contained in the supplement. Since these participants' intake is higher than that of the majority of Americans, one can presume that suboptimal levels may also exist in our patients who are otherwise "healthy."

This is not the first study that demonstrates mood improvement with B complex/vitamin C/mineral formula. Schlebusch et al showed that after 28 days of supplementation there was significantly decreased anxiety and improved sense of well-being.² In another trial of 28 days, Carroll et al found that supplementation led to improved GHQ scores and a decreased perception of stress as assessed by the PSS scale.³ In a study assessing 12 months of supplementation, Benton et al showed that there was a significant improvement in mood in females.⁴

For the practitioner of natural medicines, these results are not surprising. B complex is a foundational supplement in most protocols for our patients feeling "highly stressed." Indeed, B vitamins' reputation in helping to cope with stress is well established in the public domain as well, as evidenced by product names such as "Stress B Complex." But to what extent is supplementing with B vitamins, vitamin C, and minerals such as calcium, magnesium, and zinc a good idea for otherwise healthy adults?

What is clear is that the risk of supplementing these nutrients is negligible, but comes with significant potential benefit.

The answer to this question is unclear. What is clear is that the risk of supplementing these nutrients is negligible, but comes with significant potential benefit. While it is often espoused that a nutrient-rich diet should be able to provide all the vitamins and minerals one needs to function optimally, this study suggests otherwise. There is little debate that it is prudent for everyone to increase their intake of fruit and vegetables in an effort to consume adequate nutrients through diet. This study, along with the others that corroborate it, may be impetus for us to hedge this assumption of adequate intake with a little supplementation as well.

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REGARDING ANTIOXIDANTS

<http://www.ajcn.org/content/81/1/215S.short>

72. AMERICAN JOURNAL OF CLINICAL NUTRITION

DIETARY POLYPHENOLS AND HEALTH: PROCEEDINGS OF THE 1ST INTERNATIONAL CONFERENCE ON POLYPHENOLS AND HEALTH

Polyphenols: antioxidants and beyond

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ABSTRACT

Research on the effects of dietary polyphenols on human health has developed considerably in the past 10 y. It strongly supports a role for polyphenols in the prevention of degenerative diseases, particularly cardiovascular diseases and cancers. The antioxidant properties of polyphenols have been widely studied, but it has become clear that the mechanisms of action of polyphenols go beyond the modulation of oxidative stress. This supplemental issue of The American Journal of Clinical Nutrition, published on the occasion of the 1st International Conference on Polyphenols and Health, offers an overview of the experimental, clinical, and epidemiologic evidence of the effects of polyphenols on health.

Key Words: Polyphenols • flavonoids • antioxidants • health • cardiovascular diseases • cancers

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CITED IN 204 ARTICLES

http://www.nia.nih.gov/Alzheimers/Publications/ADProgress2005_2006/Part2/healthydiet.htm.htm

73. NATIONAL INSTITUTE ON AGING U.S. INSTITUTES OF HEALTH

A Healthy Diet May Be Important to Brain Health as Well as Body Health

EXCERPT

“A nutritious diet rich in fruits, vegetables, and whole grains and that is low in fat and added sugar can reduce the risks of many chronic conditions, including heart disease, diabetes, obesity, and some forms of cancer. In recent years, investigators have used epidemiologic, animal, and test tube studies and clinical trials to explore whether diet can play a role in preserving cognitive function or even reducing risk of AD.

A long-held theory about aging suggests that, over time, damage from free radicals (molecules that chemically react easily with other molecules) can build up in neurons, causing loss of function. This damage is called oxidative damage. The brain’s unique characteristics, including its high rate of metabolism and its long-lived neurons, may make it particularly vulnerable to oxidative damage. Previous epidemiologic and laboratory studies have suggested that fruits and vegetables that are high in antioxidants might protect the brain against this kind of damage. A group of Harvard Medical School researchers explored this possibility by examining data from more than 13,000 Nurses’ Health Study participants aged 70 and older (Kang et al., 2005).

They found that the women who ate the most vegetables—especially green leafy vegetables (like spinach and romaine lettuce) and cruciferous vegetables (like broccoli and cauliflower)—experienced a slower rate of cognitive decline than did women who ate the least vegetables. The scientists were careful to account for other factors that might influence the results, such as use of vitamin supplements, physical activity, smoking and alcohol use, and educational attainment. Interestingly, fruit consumption did not appear to be associated with any change in cognitive ability. The scientists speculate that the abundant antioxidant and folate (a nutrient that appears to be important for proper neural activity and cognitive function) content of the green leafy and cruciferous vegetables was responsible for these results.”

<http://ncp.sagepub.com/content/10/1/19.short>

SAGE JOURNALS

74. NUTRITION IN CLINICAL PRACTICE

Role of Antioxidants in Health Maintenance

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Abstract

Free radicals are produced in the body as by products of normal metabolism and as a

result of exposure to radiation and some environmental pollutants. Because they are highly reactive, they can damage cellular components and are implicated in a variety of diseases. Free radicals are normally neutralized by efficient systems in the body that include the antioxidant enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and the nutrient-derived antioxidant small molecules (vitamin E, vitamin C, carotenes, flavonoids, glutathione, uric acid, and taurine). In healthy individuals, a delicate balance exists between free radicals and antioxidants. In some pathologic conditions such as diabetes, and in critically ill patients, oxidative stress causes the level of antioxidants to fall below normal. Antioxidant supplements for such conditions are expected to be of benefit. As a preventive measure against certain diseases, the best approach for healthy individuals is to regularly consume adequate amounts of antioxidant-rich foods, eg, fruits and vegetables.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TCN-411X9Y3-H&_user=10&_coverDate=08%2F07%2F2000&_rdoc=1&_fmt=high&_orig=gateway&_origin=gateway&_sort=d&_docanchor=&view=c&_searchStrId=1740818141&_rerunOrigin=scholar.google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=bdadad9f015c9106cd6256e01e5e2081&searchtype=a

SCIVERSE-SCIENCE DIRECT

75. Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention

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Accepted 29 July 1999. Available online 24 August 2000.

Abstract

Free radicals have been implicated in over a hundred disease conditions in humans, including arthritis, hemorrhagic shock, atherosclerosis, advancing age, ischemia and reperfusion injury of many organs, Alzheimer and Parkinson's disease, gastrointestinal dysfunctions, tumor promotion and carcinogenesis, and AIDS. Antioxidants are potent scavengers of free radicals and serve as inhibitors of neoplastic processes. A large number of synthetic and natural antioxidants have been demonstrated to induce beneficial effects on human health and disease prevention. However, the structure-activity relationship, bioavailability and therapeutic efficacy of the antioxidants differ extensively. Oligomeric proanthocyanidins, naturally occurring antioxidants widely available in fruits, vegetables, nuts, seeds, flowers and bark, have been reported to possess a broad spectrum of biological, pharmacological and therapeutic activities against free radicals and oxidative stress. We have assessed the concentration- or dose-dependent free radical scavenging ability of a novel IH636 grape seed proanthocyanidin extract (GSPE) both in vitro and in vivo models, and compared the free radical scavenging ability of GSPE with vitamins C, E and β -carotene. These experiments demonstrated that GSPE is highly bioavailable and provides significantly greater protection against free radicals and free radical-induced lipid peroxidation and DNA damage than vitamins C, E and β -carotene. GSPE was also shown to demonstrate cytotoxicity towards human breast, lung and gastric adenocarcinoma cells, while enhancing the growth and viability of normal human gastric mucosal cells. The comparative protective effects of GSPE, vitamins C and E were examined on tobacco-induced oxidative stress and apoptotic cell death in human oral keratinocytes. Oxidative tissue damage was determined by lipid peroxidation and DNA fragmentation, while apoptotic cell death was assessed by flow cytometry. GSPE provided significantly better protection as compared to vitamins C and E, singly and in combination. GSPE also demonstrated excellent protection against acetaminophen overdose-induced liver and kidney damage by regulating bcl-XL gene, DNA damage and presumably by reducing oxidative stress. GSPE demonstrated excellent protection against myocardial ischemia-reperfusion injury and myocardial infarction in rats. GSPE was also shown to upregulate bcl2 gene and downregulate the oncogene c-myc. Topical application of GSPE enhances sun protection factor in human volunteers, as well as supplementation of GSPE ameliorates chronic pancreatitis in humans. These results demonstrate that GSPE provides excellent protection against oxidative stress and free radical-mediated tissue injury.

Keywords: Free radicals; Human diseases; Grape seed proanthocyanidin

<http://www.pnas.org/content/90/17/7915.short>

76. Oxidants, antioxidants, and the degenerative diseases

of aging

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PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA

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Abstract

Metabolism, like other aspects of life, involves tradeoffs. Oxidant by-products of normal metabolism cause extensive damage to DNA, protein, and lipid. We argue that this damage (the same as that produced by radiation) is a major contributor to aging and to degenerative diseases of aging such as cancer, cardiovascular disease, immune-system decline, brain dysfunction, and cataracts. Antioxidant defenses against this damage include ascorbate, tocopherol, and carotenoids. Dietary fruits and vegetables are the principal source of ascorbate and carotenoids and are one source of tocopherol. Low dietary intake of fruits and vegetables doubles the risk of most types of cancer as compared to high intake and also markedly increases the risk of heart disease and cataracts. Since only 9% of Americans eat the recommended five servings of fruits and vegetables per day, the opportunity for improving health by improving diet is great.

Again, where Dr. Null states that "...green chlorophyll-rich foods are also sources of phytonutrients, essential fatty acids, amino acids, anti-oxidants and trace minerals...." Dr. Barrett comments that: [Chlorophyll has no health-related value for humans}.

REGARDING CHLOROPHYLL

<http://jn.nutrition.org/content/135/8/1995.full>

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Nutrition and Cancer

77. **Natural Chlorophyll but Not Chlorophyllin Prevents Heme-Induced Cytotoxic and Hyperproliferative Effects in Rat Colon**

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ABSTRACT

Diets high in red meat and low in green vegetables are associated with an increased risk of colon cancer. In rats, dietary heme, mimicking red meat, increases colonic cytotoxicity and proliferation of the colonocytes, whereas addition of chlorophyll from green vegetables inhibits these heme-induced effects. Chlorophyllin is a water-soluble hydrolysis product of chlorophyll that inhibits the toxicity of many planar aromatic compounds. The present study investigated whether chlorophyllins could inhibit the heme-induced luminal cytotoxicity and colonic hyperproliferation as natural chlorophyll does. Rats were fed a purified control diet, the control diet supplemented with heme, or a heme diet with 1.2 mmol/kg diet of chlorophyllin, copper chlorophyllin, or natural chlorophyll for 14 d (n = 8/group). The cytotoxicity of fecal water was determined with an erythrocyte bioassay and colonic epithelial cell proliferation was quantified in vivo by [methyl-3H]thymidine incorporation into newly synthesized DNA. Exfoliation of colonocytes was measured as the amount of rat DNA in feces using quantitative PCR analysis. Heme caused a >50-fold increase in the cytotoxicity of the fecal water, a nearly 100% increase in proliferation, and almost total inhibition of exfoliation of the colonocytes. Furthermore, the addition of heme increased TBARS in fecal water. Chlorophyll, but not the chlorophyllins, completely prevented these heme-induced effects. In conclusion, inhibition of the heme-induced colonic cytotoxicity and epithelial cell turnover is specific for natural chlorophyll and cannot be mimicked by water-soluble chlorophyllins.

KEY WORDS: • diet • red meat • green vegetables • prevention • colon cancer

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TB1-4MY8BNY-1&_user=10&_coverDate=01%2F31%2F2007&_rdoc=1&_fmt=&_orig=search&_sort=d&_view=c&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=484af3aa699168edc7456f5ec4aed6b6

78. Nutrition Research

Volume 27, Issue 1, January 2007, Pages 1-12

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Digestion, absorption, and cancer preventative activity of dietary chlorophyll derivatives

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Received 8 June 2006; revised 11 December 2006; accepted 14 December 2006. Available online 31 January 2007.

Abstract

The growing body of epidemiological and experimental evidence associating diets rich in fruits and vegetables with prevention of chronic diseases such as cancer has stimulated interest in plant food phytochemicals as physiologically active dietary components. Chlorophyll and its various derivatives are believed to be among the family of phytochemical compounds that are potentially responsible for such associations. Dietary chlorophyll is predominantly composed of lipophilic derivatives including chlorophyll a and b (fresh fruits and vegetables), metal-free pheophytins and pyropheophytins (thermally processed fruits and vegetables), as well as Zn-pheophytins and Zn-pyropheophytins (thermally processed green vegetables). Water-soluble derivatives including chlorophyllides, pheophorbides, as well as a commercial-grade derivative known as sodium copper chlorophyllin (SCC) also contribute to the diversity of dietary chlorophyll derivatives. Although the use of chlorophyll derivatives, especially SCC, in traditional medical applications is well documented, it is perhaps the potential of chlorophyll as a cancer preventative agent that has drawn significant attention recently. Biological activities attributed to chlorophyll derivatives consistent with cancer prevention include antioxidant and antimutagenic activity, mutagen trapping, modulation of xenobiotic metabolism, and induction of apoptosis. Although most research has focused on commercial-grade SCC, the extent to which natural chlorophyll derivatives modulate biomarkers of cancer risk is also being explored. Recent research efforts have also included investigation of the impact of digestive factors on chlorophyll structure and bioaccessibility as a means to better understand the extent to which these

pigments may be bioavailable in humans and therefore have more systemic impact in the prevention of cancer.

Keywords: Chlorophyll; Chlorophyllin; Cancer prevention; Antimutagenic; Antioxidant; Xenobiotic metabolism; Apoptosis; Bioavailability

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**Third International Congress on Pigments in
Food**

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Antioxidant activity of chlorophylls and their derivatives

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Received 1 June 2004; accepted 22 February 2005. Available online 5 July 2005.

Abstract

The antioxidant activity of six natural isolated chlorophyll derivatives and Cu-chlorophyllin was investigated by measuring their protective action against lipid oxidation. For this, the β -carotene bleaching method and the stable radical 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging assay were employed. The results obtained by the β -carotene bleaching method showed that all chlorophyll derivatives presented a dose-dependent response. Pheophorbide b and pheophytin b were the strongest natural antioxidant compounds, whose activities

were comparable to BHT. The high antioxidant activity found for pheophorbide b, in comparison to pheophorbide a, demonstrated the importance of the aldehyde group for functionality. On the other hand, by the DPPH assay, all natural pigments showed low antioxidant activity when compared to Trolox. Cu-chlorophyllin, tested by both methods, presented a higher antioxidant activity than that of natural chlorophylls, showing the importance of the nature of the chelated metal in the porphyrin ring. The mechanism of antioxidant activity displayed by the natural chlorophyll derivatives does not seem to be based on the ability to donate hydrogen but maybe, on the protection of linoleic acid against oxidation and/or preventing decomposition of hydroperoxides.

Keywords: Antioxidant activity; Chlorophyll derivatives; β -carotene bleaching method; DPPH

<http://carcin.oxfordjournals.org/content/26/7/1247.full>

**80. Oxford Journals
Life Sciences & Medicine
Carcinogenesis
Volume 26, Issue 7
Pp. 1247-1255.**

Chlorophyll, chlorophyllin and related tetrapyrroles are significant inducers of mammalian phase 2 cytoprotective genes

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Received August 10, 2004.

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Abstract

Plant chlorophylls and carotenoids are highly colored, conjugated polyenes that play central roles in photosynthesis. Other porphyrins (tetrapyrroles), such as cytochromes, which are structurally related to chlorophyll, participate in redox reactions in many living systems. An unexpected new property of tetrapyrroles, including tetramethyl coproporphyrin III, tetrabenzoporphine, copper chlorin e4 ethyl ester, and of carotenoids including zeaxanthin and α -cryptoxanthin is their ability to induce mammalian phase 2 proteins that protect cells against oxidants and electrophiles. The capacity of these compounds to induce the phase 2 response depends upon their ability or that of their metabolites to react with thiol groups, a property shared with all other classes of phase 2 inducers, which show few other structural similarities. Pseudo second-order rate constants of these inducers are correlated with their potency in inducing the phase 2 enzyme NAD (P)H:quinone oxidoreductase 1 (NQO1) in murine hepatoma cells. One of the most potent inducers was isolated from chlorophyllin, a semisynthetic water-soluble chlorophyll derivative. Although chlorophyll itself is low in inducer potency, it may nevertheless account for some of the disease-protective effects attributed to diets rich in green vegetables because it occurs in much higher concentrations in those plants than the widely studied 'phytochemicals'.

And finally, Dr. Null believes that Chromium Picolinate can be helpful when a weight loss diet is indicated, while Barrett considers such supplementation a waste of time and money. The following abstracts may help you determine who is telling the truth:

REGARDING CHROMIUM PICOLINATE

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VS8-445RBF2-HG&_user=10&_coverDate=06%2F30%2F1998&_rdoc=1&_fmt=high&_orig=gateway&_origin=gateway&_sort=d&_docanchor=&_view=c&_searchStrId=1743228401&_rerunOrigin=scholar.google&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=a6a3de88b1270457109ca7549e38c779&searchtype=a

Current Therapeutic Research

81. **A randomized, double-masked, placebo-controlled study of the effects of chromium picolinate supplementation on body composition: A replication and extension of a previous study**

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Received 6 January 1998. Available online 10 October 2001.

Abstract

A previous study using a randomized, double-masked, placebo-controlled design found that supplementation with a minimum of 200 µg of chromium (in the form of chromium picolinate [CrP]) per day can lead to significant improvement in body composition (as measured by underwater testing using the displacement method). The present study used a similar design in which 122 subjects were randomized to receive either CrP 400 µg (n = 62) or placebo (n = 60). To control caloric intake and expenditure (which was not done in the first study), participants were required to monitor and maintain a log of their daily physical activity and caloric intake. Dual energy x-ray absorptiometry measurements were taken before and after the 90-day period. Analysis of the prestudy data for the two groups revealed no significant differences in any of the initial body composition variables studied. After controlling for differences in caloric intake and expenditure, as compared with the placebo group, subjects in the active treatment group lost significantly more weight (7.79 kg vs 1.81 kg, respectively) and fat mass (7.71 kg vs 1.53 kg, respectively), and had a greater reduction in percent body fat (6.30% vs 1.20%, respectively) without any loss of fat-free mass. A more conservative analysis of covariance revealed similar and statistically significant reductions in percent body fat and fat mass without any loss of fat-free mass. It was concluded that this study replicated earlier findings that supplementation with CrP can lead to significant improvements in body composition.

Author Keywords: chromium picolinate; body composition; fat mass; fat-free mass; dual energy x-ray absorptiometry.

http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6VS8-445RB0S-98&_user=10&_origUdi=B6VS8-445RBF2-HG&_fmt=high&_coverDate=12%2F31%2F1996&_rdoc=1&_orig=article&_origin=article&_zone=related_art&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=29aef6d1247a2912a5726ac18110ed7d

Current Therapeutic Research

Volume 57, Issue 10, 1996, Pages 747-756

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82. **Effects of chromium picolinate supplementation on body composition: a randomized, double-masked,**

placebo-controlled study

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Received 22 July 1996. Available online 10 October 2001.

Abstract

To examine the effect of chromium picolinate (CrP) on body composition, a randomized, double-masked, placebo-controlled study was conducted. A total of 154 patients received either a placebo or 200 µg or 400 µg of CrP per day. Subjects were asked to consume at least two servings of a protein/carbohydrate nutritional drink a day that contained the different amounts of CrP. Subjects were free-living and were not provided with weight loss, dietary, or exercise guidance. Body composition was measured before and after the 72-day test period by using underwater testing (displacement method) with residual lung volumes determined by helium dilution. On completion of the posttest, a body composition improvement (BCI) index was calculated for each subject by adding the loss of body fat and gain in nonfat mass and subtracting fat gained and lean lost. Analysis of the prestudy data revealed that there were no significant differences in body composition between the three groups. After the test period, both the 200-µg and 400-µg groups had significantly higher positive changes in BCIs compared with placebo. A single-factor analysis of variance weighted linear trend was also highly significant. No significant differences in BCI were found between the 200- and 400-µg groups. Supplementation with a minimum of 200 µg/d of chromium (as CrP) can lead to significant improvement in body composition.

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Chromium Picolinate Supplementation Attenuates Body Weight Gain and Increases Insulin Sensitivity in Subjects With Type 2 Diabetes

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Abstract

OBJECTIVE—Chromium picolinate (CrPic) supplementation has been suggested to improve glycemia, but there are conflicting reports on efficacy. We sought to determine the effect of CrPic on insulin sensitivity, glycemic control, and body composition in subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS—Thirty-seven subjects with type 2 diabetes were evaluated. After baseline, subjects were placed on a sulfonylurea (glipizide gastrointestinal therapeutic system 5 mg/day) with placebo for 3 months. Subjects were then randomized in a double-blind fashion to receive either the sulfonylurea plus placebo (n = 12) or the sulfonylurea plus 1,000 µg Cr as CrPic (n = 17) for 6 months. Body composition, insulin sensitivity, and glycemic control were determined at baseline, end of the 3-month single-blind placebo phase, and end of study.

RESULTS—Subjects randomized to sulfonylurea/placebo, as opposed to those randomized to sulfonylurea/CrPic,

had a significant increase in body weight (2.2 kg, $P < 0.001$ vs. 0.9 kg, $P = 0.11$), percent body fat (1.17%, $P < 0.001$ vs. 0.12%, $P = 0.7$), and total abdominal fat (32.5 cm², $P < 0.05$ vs. 12.2 cm², $P < 0.10$) from baseline. Subjects randomized to sulfonylurea/CrPic had significant improvements in insulin sensitivity corrected for fat-free mass (28.8, $P < 0.05$ vs. 15.9, $P = 0.4$), GHb (-1.16%, $P < 0.005$ vs. -0.4%, $P = 0.3$), and free fatty acids (-0.2 mmol/l, $P < 0.001$ vs. -0.12 mmol/l, $P < 0.03$) as opposed to sulfonylurea/placebo.

CONCLUSIONS—This study demonstrates that CrPic supplementation in subjects with type 2 diabetes who are taking sulfonylurea agents significantly improves insulin sensitivity and glucose control. Further, CrPic supplementation significantly attenuated body weight gain and visceral fat accumulation compared with the placebo group.

<http://www.jacn.org/content/17/6/544.abstract>

JOURNAL OF THE AMERICAN COLLEGE OF NUTRITION

83. Chromium Research from a Distance: From 1959 to 1980

Walter Mertz, MD

Author Affiliations

Former Director of the Human Nutrition Center, USDA, Beltsville, Maryland (Retired)

Abstract

More than 50 years of work have led to the recognition of trivalent chromium as an essential element. Shortly after its identification as an essential element in 1959, its interaction with insulin in vitro and in vivo was established, and the site of action identified as the insulin-sensitive cell membrane. Despite other early clinical successes with chromium supplementation, four major problems have influenced the rate of progress since then: 1) chromium analysis; 2) interaction of chromium with other dietary factors; 3) diagnosis of chromium status; and 4) other controversies, such as the carcinogenic potential of chromium (since disproved) and the lack of an effect on glucose tolerance even in chromium deficient organisms (now explained). These controversies have mostly dissipated as new knowledge integrated seemingly irreconcilable facts and opinions. It is now known that chromium may potentiate the action of insulin either by an effect on insulin dependent functions, or by maintaining these functions with less insulin, or by a combination of both. Despite much progress in the last 30 years, major challenges in chromium research remain, such as the development of practical methods for diagnosing chromium deficiency. Of several approaches for solving this problem, the most feasible might be to standardize the urinary

chromium response following an insulinogenic challenge, such as an oral load of glucose or of glucose plus fructose (for maximal stimulation) with urine collection before and during the 2-hour test.

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84. **A randomized, double-masked, placebo-controlled study of the effects of chromium picolinate supplementation on body composition: A replication and extension of a previous study**

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Abstract

A previous study using a randomized, double-masked, placebo-controlled design found that supplementation with a minimum of 200 µg of chromium (in the form of chromium picolinate [CrP]) per day can lead to significant improvement in body composition (as measured by underwater testing using the displacement method). The present study used a similar design in which 122 subjects were randomized to receive either CrP 400 µg (n = 62) or placebo (n = 60). To control caloric intake and expenditure (which was not done in the first study), participants were required to monitor and maintain a log of their daily physical activity and caloric intake. Dual energy x-ray absorptiometry measurements were taken before and after the 90-day period. Analysis of the prestudy data for the two groups revealed no significant differences in any of the initial body composition variables studied. After controlling for differences in caloric intake and expenditure, as compared with the placebo group, subjects in the active treatment group lost significantly more weight (7.79 kg vs 1.81 kg, respectively) and fat mass (7.71 kg vs 1.53 kg, respectively), and had a greater reduction in percent body fat (6.30% vs 1.20%, respectively) without any loss of fat-free mass. A more conservative analysis of covariance revealed similar and statistically significant reductions in percent body fat and fat mass without any loss of fat-free mass. It was concluded that this study replicated earlier findings that supplementation with CrP can lead to significant improvements in body composition.

Author Keywords: chromium picolinate; body composition; fat mass; fat-free mass; dual energy x-ray absorptiometry.

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85. Effects of chromium picolinate supplementation on body composition: a randomized, double-masked, placebo-controlled study

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RESULTS—Subjects randomized to sulfonylurea/placebo, as opposed to those randomized to sulfonylurea/CrPic, had a significant increase in body weight (2.2 kg, P < 0.001 vs. 0.9 kg, P = 0.11), percent body fat (1.17%, P < 0.001 vs. 0.12%, P = 0.7), and total abdominal fat (32.5 cm², P < 0.05 vs. 12.2 cm², P < 0.10) from baseline. Subjects randomized to sulfonylurea/CrPic had significant improvements in insulin sensitivity corrected for fat-free mass (28.8, P < 0.05 vs. 15.9, P = 0.4), GHb (−1.16%, P < 0.005 vs. −0.4%, P = 0.3), and free fatty acids (−0.2 mmol/l, P < 0.001 vs. −0.12 mmol/l, P < 0.03) as opposed to sulfonylurea/placebo.

CONCLUSIONS—This study demonstrates that CrPic supplementation in subjects with type 2 diabetes who are taking sulfonylurea agents significantly improves insulin sensitivity and glucose control. Further, CrPic supplementation significantly attenuated body weight gain and visceral fat accumulation compared with the placebo group.

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EFFICACY OF 12 WEEKS SUPPLEMENTATION OF A BOTANICAL EXTRACT BASED WEIGHT LOSS FORMULA ON BODY WEIGHT, BODY COMPOSITION AND BLOOD CHEMISTRY IN HEALTHY, OVERWEIGHT SUBJECTS—

A RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL

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Abstract

Objective: The aim of this study was to evaluate the efficacy and safety of composite extracts in reducing weight, as the main outcome measure.

Secondary measures of the study were body composition change.

Design: Randomised, double blind, placebo-controlled clinical trial.

Setting: Tertiary university clinic.

Subjects: hundred and five subjects, 5 of them withdrawn consent, 2 drop-outs not related to study preparation.

Intervention:

Two tablet per meal concept supposed to generate a “psychological” therapy-like approach during 12 weeks supported by measured physical activity. The tablets 1 (one hour before meals, comprises extracts of Asparagus, Green tea, Black tea, Guarana, Mate and Kidney beans) and 2 (taken half an hour after meals, comprises extracts of Kidney bean pods, Garcinia cambogia, and Chromium yeast) are taken twice daily with two main meals.

Results:

A significant change of the Body Composition Improvement Index (BCI) was observed in the active extract group compared to placebo ($p = 0.012$). Weight, BMI, waist-to-hip ratio was not statistically different between groups. Body fat loss was greater in active group ($p = 0.011$) compared to placebo. A weight loss parameter corrected for exercise was introduced and found to be higher in active group ($p = 0.046$) than in placebo, meaning that the formula was more efficacious, due to a concurrently performed exercise program – a recommended strategy for life style modification.

Conclusions:

A significant change of the Body Composition Improvement Index and the decrease in body fat was statistically significant in active extract subjects compared to placebo. A change in some outcome measures like: weight, BMI failed to produce significant difference between groups.

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