
Insomnia:
The Unusual Suspects

Oh Say, Can You Sleep?

- National Institutes of Health (NIH) - [1]70 million Americans experience sleep disorders.
  - Half of this group have chronic sleep problems
- National Sleep Foundation (NSF) - [2]58% of adults in the U.S. experience symptoms of insomnia a few nights a week or more.

The Cost of Insomnia

- NSF estimates[2]:
  - $14 billion annually for insomnia
  - Additional $28 billion for related consequences

Insomnia: Related Consequences

- [1]Worsens diseases such as diabetes and high blood pressure
- [5]Aggravates or causes anxiety and depression
- [1]Reduces work productivity

1995 US Government Study[3]

- 100,000 police-reported motor vehicle
- 1,550 deaths and 71,000 injuries
- $12,500,000,000 in diminished productivity and property loss
- Maggie's Law

Current Knowledge: Causes of Insomnia

National Heart, Lung, and Blood Institute[5]:

- Advanced age (>=60)
- Female gender
- Depression
- Chronic stress
- Environmental noise or extreme temperatures.
- Medication side effects
- Misuse of caffeine, alcohol, cigarettes, or other substances

Looking for Alternatives

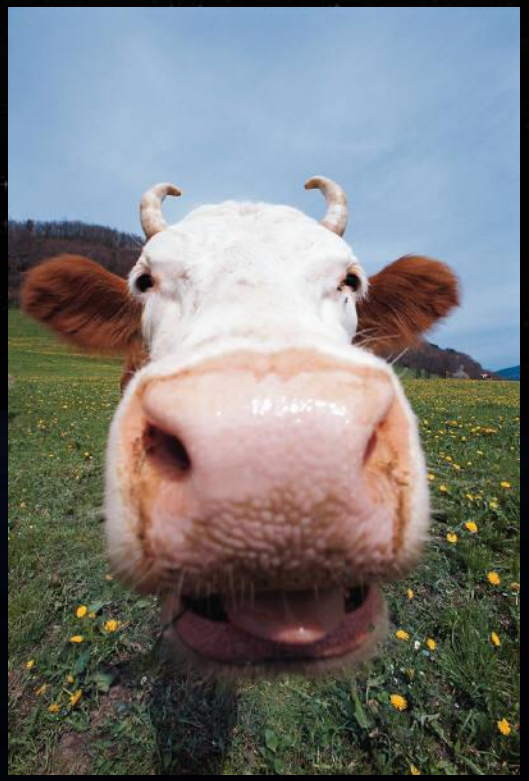
The National Center for Complementary and Alternative Medicine (NCCAM)[1]:

- Valerian – University of Washington, Emory University, University of Virginia
- Yoga and relaxation exercises - Brigham and Women's Hospital
- Hops - University of Chicago
- Vitamin B12 - Brigham and Women's Hospital
- Melatonin - University of Pennsylvania
- High-intensity light - University of North Carolina
- Homeopathy - University of Arizona

New Potential Suspects

- F Excess Dietary Protein
- F Cooked Foods
- F Magnesium Deficiency
- F Oral Contraceptives

Dietary Protein



USDA Daily Protein Recommendation[7]

Women:
19- 30 yrs- 5 1/2 ounce equivalents
31-50+ yrs old - 5 ounce equivalents

Men:
19-30 yrs - 6 1/2 ounce equivalents
31-50 yrs - 6 ounce equivalents
51+ yrs - 5 1/2 ounce equivalents

Excess Protein Consumption

- F 2002 - total meat consumption (red meat, poultry, and fish) was 200 pounds per person[4]
  - F 23 pounds above the level in 1970.
- F [6]Dairy - 5%.

Dietary Protein: Tryptophan and Tyrosine[8]

- Nine overnight-fasted subjects consumed(3-7 days apart)
  - Carbohydrate-rich (69.9 g carbohydrate and 5.2 g protein) breakfast
  - Protein-rich (15.4 g carbohydrate and 46.8 g protein) breakfast
- Blood samples were assayed for tryptophan and tyrosine

Dietary Protein: Tryptophan and Tyrosine[8]

Results: (each $P < 0.01$)

- Median difference for tryptophan: LNAA ratio was 54% (range: 36-88%)
- Median difference for tyrosine: LNAA was 28% (range: 10-64%)

Dietary Protein: Sequential Meals[9]

- Fasted rats ingested a carbohydrate meal followed 2 hrs later by a high protein meal
- Other rats ingested a high protein meal first, followed by a carbohydrate meal

Dietary Protein: Sequential Meals[9]

Results:

- Carbohydrate first, tryptophan and serotonin synthesis increased after 2 hrs
  - Reversed after 4 hrs if the second meal contained protein
- Protein first, no changes in brain tryptophan or serotonin after 2 hrs
  - Second carbohydrate meal after 2 hrs did not raise brain tryptophan or serotonin

Dietary Protein: Dopamine and Norepinephrine

- Increases dopamine[27]
- Increases norepinephrine[28]

Cooked Foods

Beta-Carbolines[14]

- A type of indole alkaloid chemically similar in structure to tryptophan
- Metabolize to mitochondrial toxicants

Beta-Carboline Exposure[15]

- Low concentrations
  - Low processed foods (milk, yogurt, raw meats, and fish)
- Relatively high concentrations
  - Well-done cooked meat and fish (57-160 ng g(-1))
  - Highest amounts in brewed coffee (29-207 microg l(-1))
  - Fermented alcoholic beverages (n.d.-41 mug l(-1))

Beta-Carbolines and Serotonin

- Structurally related 1,2,3,4-tetrahydro-beta-carbolines bind at 5-HT(5A) receptors[11]
- All examined derivatives also possess affinity for 5-HT(2A) receptors[12]

Magnesium Deficiency

Magnesium Deficiency: Potential Causes

- F Low dietary intake[25]
- F Alcoholism[29]
- F Anorexia[29]
- F Severe diarrhea[29]
- F Malabsorption[29]

Magnesium Deficiency: Sleep Connection[26]

- Magnesium plays a key role in insulin regulation
- Insulin aids in regulating serotonin

Magnesium Deficiency: Biorhythms[17]

- Low Mg intake associated with various deregulating biorhythms
  - Increased melatonin leads to depression
  - Decreased melatonin leads to insomnia

Magnesium Deficiency: Depression[16]

Case studies:

- Rapid recovery (less than 7 days) from major depression using 125-300 mg of magnesium at each meal
  - Glycinate and taurinate forms

- Related disorders treated with Mg: insomnia and sleeplessness

Oral Contraceptives

Oral Contraceptives: Serotonin[20]

- 30 women using oral contraceptive steroids for 2 to 5 years
- 24 hour urinary excretion tests for
  - Serotonin metabolites
  - Tryptophan metabolite
  - Adrenal metabolites

Oral Contraceptives: Serotonin[20]

Result:

- Oral contraceptive use was correlated with depression in the depression group
- No correlation in the control group

Oral Contraceptives: Stress[22]

- 102 females using oral contraceptives
- Subjects under high stress
- Control group with low stress

Oral Contraceptives: Stress[22]

Results:

- High stress subjects:
  - Significant decrease of insulin and tryptophan in relation to other LNAAs
- Low stress subjects:
  - No relationship between insulin and tryptophan to other LNAAs or mood

Conclusion

The existing evidence suggests that

- Excess dietary protein:
  - Impairs serotonin production and increases excitatory neurotransmitters
- Cooked food beta-carbolines:
  - Block serotonin function by binding to serotonin receptors
- Magnesium deficiency:
  - Impairs the biorhythm and the insulin/serotonin connection
- Oral contraceptives:
  - May reduce tryptophan levels in susceptible women

References

1. Can't Sleep? Science Is Seeking New Answers http://nccam.nih.gov/news/newsletter/2005_summer/sleep.htm accessed June 25, 2006

2. Can't Sleep? Learn About Insomnia http://www.sleepfoundation.org/hottopics/index.php?secid=9&id=215 accessed June 25, 2006

3. Maggie's Law: National Drowsy Driving Act of 2003 http://www.theorator.com/bills108/hr968.html accessed June 25, 2006

4. Food Consumption: Overview http://www.ers.usda.gov/briefing/consumption/overview.htm accessed June 25, 2006

References

5. Facts About Insomnia
http://www.nhlbi.nih.gov/health/public/sleep/insomnia.htm accessed June 25, 2006.

6. U.S. Food Consumption Up 16 Percent Since 1970
http://www.ers.usda.gov/AmberWaves/November05/Findings/USFoodConsumption.htm accessed June 25, 2006

7. How much food from the meat & beans group is needed daily?
http://www.mypyramid.gov/pyramid/meat_amount.aspx

8. Wurtman RJ. Wurtman JJ. Regan MM. McDermott JM. Tsay RH. Breu JJ. Effects of normal meals rich in carbohydrates or proteins on plasma tryptophan and tyrosine ratios. American Journal of Clinical Nutrition. 77(1):128-32, 2003 Jan.

References

9. Fernstrom MH. Fernstrom JD. Brain tryptophan concentrations and serotonin synthesis remain responsive to food consumption after the ingestion of sequential meals. [Journal Article] American Journal of Clinical Nutrition. 61(2):312-9, 1995 Feb..

10. Fernstrom JD. Acute and chronic effects of protein and carbohydrate ingestion on brain tryptophan levels and serotonin synthesis. [Journal Article] Nutrition Reviews. 44 Suppl:25-36, 1986 May.

11. Grella B. Teitler M. Smith C. Herrick-Davis K. Glennon RA. Binding of beta-carbolines at 5-HT(2) serotonin receptors. [Journal Article] Bioorganic & Medicinal Chemistry Letters. 13(24):4421-5, 2003 Dec 15.

12. Khorana N. Smith C. Herrick-Davis K. Purohit A. Teitler M. Grella B. Dukat M. Glennon RA. Binding of tetrahydrocarboline derivatives at human 5-HT5A receptors. [Journal Article] Journal of Medicinal Chemistry. 46(18):3930-7, 2003 Aug 28

References

13. Gu YS, Kim IS, Park JH, Lee SH, Park DC, Yeum DM, Ji CI, Kim SH, Wakabayashi K, Kim SB. Effects of seasoning and heating device on mutagenicity and heterocyclic amines in cooked beef. Biosci Biotechnol Biochem. 2001 Oct

14. Ostergren A, Annas A, Skog K, Lindquist NG, Brittebo EB. Long-term retention of neurotoxic beta-carbolines in brain neuromelanin. J Neural Transm. 2004 Feb.

15, Herraiz T. Relative exposure to beta-carbolines norharman and harman from foods and tobacco smoke. Food Addit Contam. 2004 Nov.

16. Eby GA, Eby KL. Rapid recovery from major depression using magnesium treatment. Med Hypotheses. 2006

References

17. Durlach J, Pages N, Bac P, Bara M, Guiet-Bara A, Agrapart C. Chronopathological forms of magnesium depletion with hypofunction or with hyperfunction of the biological clock. Magnes Res. 2002 Dec.

18. Takahashi H, Imai K, Katanuma A, Sugaya T, Hisano K, Motoya S, Aoki S, Sugiyama T, Yachi A. A case of chronic fatigue syndrome who showed a beneficial effect by intravenous administration of magnesium sulphate.ß Arerugi. 1992 Nov.

19. Hornyak M. Voderholzer U. Hohagen F. Berger M. Riemann D. Magnesium therapy for periodic leg movements-related insomnia and restless legs syndrome: an open pilot study. [Clinical Trial. Journal Article] Sleep. 21(5):501-5, 1998 Aug 1

20. Shaarawy M. Fayad M. Nagui AR. Abdel-Azim S. Serotonin metabolism and depression in oral contraceptive users. [Journal Article] Contraception. 26(2):193-204, 1982 Aug

References

21. Baker JM. Bond SW. Handley SL. Effects of long-term treatment with contraceptive steroids on plasma and brain tryptophan, brain 5-hydroxytryptamine, and locomotor activity in female mice [proceedings]. [Journal Article] British Journal of Pharmacology. 59(3):531P-532P, 1977 Mar.

22. Tuiten A, Panhuysen G, Koppeschaar H, Fekkes D, Pijl H, Frolich M, Krabbe P, Everaerd W. Stress, serotonergic function, and mood in users of oral contraceptives. Psychoneuroendocrinology. 1995

23. Prothro J. Any depression from OC-altered vitamin B6 levels? [Answer to question of Jan Marquand] Contracept Technol Update. 1981 Sep.

24. Parry BL, Rush AJ. Oral contraceptives and depressive symptomatology: biologic mechanisms. Compr Psychiatry. 1979 Jul-Aug

References

25. Morgan KJ, Stampley GL, Zabik ME, Fischer DR. Magnesium and calcium dietary intakes of the U.S. population. J Am Coll Nutr. 1985;4(2):195-206.

26. Takaya J, Higashino H, Kobayashi Y. Intracellular magnesium and insulin resistance. Magnes Res. 2004 Jun;17(2):126-36.

27. During MJ. Acworth IN. Wurtman RJ. Effects of systemic L-tyrosine on dopamine release from rat corpus striatum and nucleus accumbens. [Journal Article] Brain Research. 452(1-2):378-80, 1988 Jun 14.

28. Yokogoshi H. Effect of dietary level of protein or methionine and threonine on the amino acids and catecholamines in brain of rats fed a high tyrosine diet. [Journal Article] Journal of Nutritional Science & Vitaminology. 31(5):519-31, 1985 Oct.

29. Whang R. Magnesium deficiency. Causes and clinical implications.Drugs. 1984 Oct;28 Suppl 1:143-50.