April 1997 Issue | Dr.Selenium

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This month in *Functional Medicine Update*, it is a pleasure to have as Clinicians of the Month Dr. Jonathan Wright and Dr. Alan Gaby, two well-known experts in the field of nutritional medicine. Every time they were on *PMU* (as *Functional Medicine Update* was called in the past), their interviews were hailed as some of the most clinically interesting Clinician of the Month interviews we had. You will not be disappointed this month with the information Dr. Wright and Dr. Gaby share.

I want to discuss some specific areas this month and talk about them with Drs. Wright and Gaby. The first has to do with some of the recent news about amino acid analysis and the value of looking at amino acids in plasma or urine as prognostic markers. I will weave this theme through several topics on this month's *Functional Medicine Update*.

Second, I will talk about the relationship of antioxidants to certain risk factors and give you an update on some of the mechanisms in clinical application, as well as some "tricks" that are emerging about using antioxidants effectively in clinical practice. Third, there will be a preview of current information on obesity, new understanding about weight management, and leptin and insulin insensitivity.

Let's begin by discussing risk factors to ischemic stroke and its relationship to excitotoxic amino acids. A number of years ago, Dr. John Olney, a neurotoxicologist, said there were certain amino acids that could induce a neurotoxic effect, particularly in sensitive individuals, like children. Amino acids, like glutamate and aspartate, at high levels could be seen as neuroexcitotoxic amino acids that could overly stimulate receptor sites on the neurons related to neuroexcitation.

A recent *Lancet* (1997;349:97) contained a report of an interesting study looking at 556 consecutive emergency unit admissions of individuals who had suffered ischemic stroke. In this study, the authors found a close correlation between elevated levels of the amino acid glutamate in plasma and later appearance of acute stroke. They suggest that one of the first steps related to initiation of ischemic stroke is the increased level of the excitotoxic amino acid glutamate in plasma and cerebral spinal fluid, which precedes the actual onset of the stroke by 48 hours or longer. This is an indication, once again, that the various amino acids that control neuroexcitation and neurological function may be markers for various aspects of neurologic function.

The N-methyl-D-aspartate receptor site on the surface of neurons regulates the ionophoric activity across the neuronal membrane and results in an influx of calcium into the cell. This calcium influx results in activation of the inducible form of nitric oxide synthase, which produces nitric oxide from arginine. Nitric oxide can combine with superoxide to form peroxynitrite.

In addition, an N-methyl-D-aspartate pathway is the receptor site on the surface of neurons. It codes for the ionophoric activity across the membrane where calcium can be taken up across the membrane, entering into the cell, resulting in an activation of the inducible form of nitric oxide synthase, and producing nitric oxide from the amino acid arginine within the cell. It then can combine with superoxide to form peroxynitrite, and an oxidant stress redox shift occurs, which then uncouples mitochondrial function and leads to increased apoptotic damage to the neuron.

What this explanation basically says is that neuroexcitotoxicity relates to neuronal burnout. As Dr. Sian stated in his article on Parkinson's disease in the *Journal of Neurology* last year, "It is as if the brain is on fire." The elevated levels of certain neuroexcitotoxic amino acids, like glutamate may therefore, indicate alteration in this activation pathway and signal progressive changes that later can be seen as stroke. This is an interesting new view of how our neurologic system maintains balance between arousal and in

Another amino acid in the news is the tryptophan metabolite melatonin. Melatonin is an interesting messenger molecule. It is actually in itself not an amino acid (its structure is N-acetyl-5-methoxytryptamine), but it is a derivative of the amino acid tryptophan. Three centuries ago, the French philosopher Renè Descartes described the pineal gland as the "seat of the soul," but it was not until the late 1950s that melatonin, a principal substance secreted by the pineal gland, was identified. You may have seen in the *New England Journal of Medicine* a recent article, "Melatonin in Humans" (1997;336:186), in which the author discusses the physiology and pharmacology of the pineal hormone melatonin.

First identified in bovine pineal extracts on the basis of its ability to aggregate melanin granules and lighten the color of frog skin, melatonin has more recently been found to be important as a light/dark circadian rhythm hormone, secreted by the pineal gland, that has impact upon sleep, mood, sexual maturation, and reproduction, and it may also have anti-proliferative effects within the body's immune response and effects on biological aging. It appears to increase the propensity for sleep, and it has a hypothermic effect at pharmacological doses. In circadian rhythm, it appears to control the light/dark cycle, and it resets the biological clock of the body. It appears to have a role in cyclic mood disorders, such as seasonal affective disorder (SAD) and certain forms of depression. It also appears to inhibit the reproductive process and has a close relationship with estrogen balance in women. This may explain some of the differences in reproductive and menstrual cycles in women who live in northern latitudes where there is much more darkness

Darkness has an adverse effect on secretion of melatonin by the pineal gland. We know that light plays a principal role in inhibiting the secretion of melatonin, and darkness stimulates its secretion. Melatonin has an effect on blocking estrogen secretion. We can talk about normal light/dark conditions and their relationship to the biological clock; but as melatonin is increased, there is a move in the circadian rhythm toward sleep, and there is also an alteration in metabolic activity. In the brain, melatonin apparently serves as a free radical scavenger.

Dr. Russell Reiter has done extraordinary research on melatonin as an antioxidant. Melatonin seems to be more effective than other known antioxidants, such as mannitol, glutathione, and vitamin E, in protecting against oxidative damage. Therefore, melatonin may provide protection against diseases that cause degeneration or proliferative changes by shielding macromolecules in the nervous system, particularly DNA, from oxidative injuries. This ongoing area of research suggests that during sleep melatonin plays

an important role as a brain antioxidant and that sleep has a reparative effect upon brain chemistry in some sense.

The *NEJM* article points out there are many studies on the effects of exogenous melatonin on sleep. In 1974, Cramer et al. were the first to report, in a study of 15 normal subjects, that a single dose of 50 mg intravenously of melatonin resulted in decreased latency of sleep onset. In 1981, Vollrath studied 10 subjects given a single dose of 1.7 mg of melatonin intranasally during daytime, which induced sleep. In 1984, Lieberman did a study with 14 normal subjects with a total dose of 240 mg of melatonin intravenously, 80 mg given three times over a two-hour period. This was during daytime, and it reduced alertness and increased fatigue and sleepiness. In light of work today on this melatonin relationship, 80 mg given three times would be considered extraordinarily high. In 1991, Dahlitz et al. studied eight patients with delayed sleep phase syndrome, administered a single dose of 5 mg orally, given at 10 p.m. for four weeks. They had an earlier onset of sleep and wakeup time in this study.

In 1995, Haimov, et al. studied 26 elderly subjects with insomnia, with a single 2 mg dose given orally. It was a sustained-release dose in one group and fast-release in another, given two hours before bedtime for a week. There was increased efficiency and duration of sleep in the sustained-release group and improved initiation of sleep in the fast-release group, suggesting a kinetic relationship of uptake and utilization of melatonin. Garfinkel did a study in 1995 with 12 elderly subjects with insomnia, again, a single dose of 2 mg orally, given at night for three weeks, which resulted in increased efficiency of sleep. Oldani et al., in a 1994 study with six patients with delayed sleep phase syndrome, administered a single dose of 5 mg orally for one month, with the advanced onset of sleep.

In 1994, Dollins gave 20 young subjects a single dose of 0.1 to 0.3 mg orally at midday, with increased duration of sleep and decreased sleep onset latency. Zhdanova et al., in 1995, gave six young subjects a single dose of 0.3 to 1 mg orally, at either 6, 8, or 9 p.m., which decreased sleep onset latency and had no effect on REM sleep. Finally, in 1995, Wurtman and Zhdanova conducted a study in which nine elderly subjects with insomnia were given a single dose of 0.3 mg orally, 30 minutes before bedtime, which resulted in increased efficacy of sleep and decreased sleep onset latency. So, the therapeutic dose range of melatonin in sleep disorders is anywhere from as low as 0.3 mg in these studies to as high as 5 mg.

The message seems to be that ranges between .3 and 1 mg appear to have efficacy when given about an hour before bedtime

In the area of sexual maturation and reproduction, melatonin again seems to play an important role, particularly in women, in estrogen balance. Melatonin secretion does not change during the menstrual cycle in normal women. Substantial increases in serum estradiol concentrations do not alter melatonin secretion in fertile women with normal cycles. On the other hand, serum melatonin concentrations are increased in women with hypothalamic amenorrhea. In animals that breed seasonally, melatonin inhibits pituitary responses to gonadotrophic-releasing hormone, or its pulsatile secretion. It seems, therefore, that melatonin does, in fact, have a fairly profound influence on hormone levels. In one study of normal young women, a very large daily dose of melatonin (this was certainly a therapeutic dose, around 300 mg), given orally for four months, suppressed the midcycle surge and luteinizing hormone secretion and partially inhibited ovulation, and the effects were enhanced by concomitant administration of a progestin. In some countries, melatonin is being used partly as a birth control agent, so it does have some profound effects on pituitary hormones and secondary ovarian hormones.

The conclusion from all of this is that melatonin seems to have a profound influence on sleep cycles. There is no evidence to support the contention that it has a hypnotic effect. Its peak serum concentrations coincide with sleep; its administration in doses that raise the serum concentration to levels that normally occur nocturnally can promote and sustain sleep; higher doses also promote sleep, possibly by causing relative hypothermia. Exogenous melatonin can influence circadian rhythms, thereby altering the timing of fatigue and sleep. Abnormally higher pharmacologic concentrations of melatonin in women are associated with altered ovarian function and ovulation. It is tempting to speculate, according to this article, that the hormone has an anti-gonadal or anti-ovulatory effect in humans, as it does in some seasonal and non-seasonal mammalian breeders, but this possibility has not yet been substantiated in humans. The anti-proliferative and anti-aging effects of melatonin are even more problematic at this time, and in using melatonin to obtain any of these effects, one needs to proceed with caution, given its profound influence on brain chemistry and neurochemical function.

When we look at tryptophan/melatonin interrelationships to sleep and mood alteration, we can conclude there are things here that are worthy of inspection, but certainly, using higher doses of above 5 mg, is a problematic area, and doses between 0.3 and 1 mg given before bed might have an effect on reducing sleep latency and improving sleep in individuals with various forms of insomnia.

We have also had continued discussion about antioxidants. The antioxidants I would like to focus on clinically are vitamin C, zinc in regard to its activity with superoxide dismutase, catechins from various phytonutrient-rich products, and polyphenols from various plant foods

Another interesting paper relates to the green tea story and its association to the red wine/French paradox story. (The red wine story is that the French, who seem to eat a very high level of fat in their diet, also consume large amounts of red wine, which is rich in these polyphenols, and it has been suggested this may account for their lower incidence of heart disease. There is a controversy over interpretation of the French paradox data, but the story about polyphenols, red wine, and grape juice is important.) A paper published in *Science*magazine (1997;275:218) described a study at the Department of Medical Chemistry and Pharmacognosy, College of Pharmacy, University of Illinois in Chicago, in collaboration with Dr. Farnsworth, a highly respected pharmacognosist at the University of Illinois. This particular paper reports the activity of an antioxidant derived from grapes, which is a polyphenol phytoalexin called resveratrol.

Found in grapes and other food products, resveratrol has been purified and shown to have very powerful anticarcinogenic activity in assays representing three major stages of carcinogenesis. It was found to act as an antioxidant and an antimutagen and to induce phase II drug-metabolizing enzymes. These include the quinone reductase activities and the glutathione conjugation activities, so it is a phase II upregulator. It also inhibited cyclooxygenase 2 and hydroperoxide formation, so it was also an anti-inflammatory agent. In model studies, it had the ability to block cyclooxygenase, and it had an effect on lipoxygenase, which means that it slowed down the formation of the proinflammatory 2-series prostaglandins. It also prevented the formation of the leukotrienes, and it had a positive effect on upregulating phase II detoxification enzymes.

The results of this study seem to be consistent with epidemiological studies that have suggested coronary heart disease mortality could be decreased by consuming red wine that contains these polyphenols. Resveratrol may play a role in prevention of heart disease and certain forms of carcinogen-induced cancer. It also was found that resveratrol seems to lower, or inhibit, platelet aggregation and coagulation.

Obviously, it may alter eicosanoid 2-series synthesis and favorably modulate lipoprotein metabolism.

The ultimate conclusion, obviously, is that this substance deserves further evaluation, and foods and nonalcoholic beverages derived from grapes should be considered dietary sources of this important antioxidant and modulator of gene expression. The resveratrol study is another example of the increasing number of papers discussing the therapeutic benefit of phytonutrients, their relationship to antioxidants, and their function as gene expression modulators

INTERVIEW TRANSCRIPT

The Selenium Story

JB: I know you both have had quite a bit of historical experience and interest in the trace mineral nutrition area. One trace mineral in the news is selenium, The *New England Journal of Medicine* and *JAMA* have published papers on selenium recently. Could you tell us how you see the emerging selenium story, its relationship to immune protection and antioxidant effects, and how it fits into nutritional medicine?

JW: Thank you for having us on *Functional Medicine Update* this month, Jeffrey. Before I begin to discuss the selenium question -- I'll cover the immune protection, and I'm sure Alan will chime in on the antioxidants -- I'll say that you were modest in not mentioning that Alan's first chaired professorship is the Jeffrey Bland Chair at Bastyr University, and all of us in the natural medicine community really appreciate you making that possible, an endowed chair at Bastyr. Thank you very much.

The selenium story has been percolating along in small studies here and there, as just possibly being an anticancer item, and just possibly being an antiviral item. A lot of this research has been drawn together by several people, but one of the people I've talked to the most is Professor Taylor at the University of Georgia, Computational Center for Molecular Genetics.

The way this gets into clinical practice is really not as complicated as it sounds. Dr. Taylor explains that, in sequencing the genetics of certain viruses, he came to the conclusion, just by the mathematics of the sequences, that these viruses were coded for the production of a selenoprotein. He really had some puzzle as to what this was doing there. To shorten this up, he's made a prediction that the selenoproteins produced by certain viruses actually act as brakes on the virus' reproduction or, to put it another way, the virus makes its own "birth control pill." However, when there is insufficient selenium around, the virus does not make this selenoprotein, so the birth control pill it makes for itself is not there and the virus goes wild. This, as Dr. Taylor says, gives us an effective way of helping the people we're working with "live with" their viruses better.

Even if we can't totally eradicate the virus in the body, if we can put it to sleep, as it were, then it's just not going to bother us so badly. There was a research paper published, from North Carolina I believe, which showed that the coxsackie virus, an otherwise benign virus, suddenly became quite virulent when it was run through animals that were selenium insufficient, and, in fact, it killed a lot of experimental animals. After that, even when it was run through selenium-sufficient animals, it remained virulent. So

apparently the lack of selenium and the lack of production of this repressor, or whatever it is, allowed the virus to go bad. There have been other studies on selenium showing, for example, that if one puts 15 parts per million (which isn't very much) of selenium into table salt and gives it to one group of folks over in China, and another group doesn't get any selenium in their table salt, the incidence of hepatitis goes way down in the group that gets selenium. The viruses that are inhibited by selenium, or that inhibit themselves in selenium, are the retrovirus group. This happens to include HIV, and it has created a great stir. It also applies to just about all the other retroviruses, particularly the whole herpes family. For example, I found that adding sodium selenide at 250 mcg twice daily to the program of people who have recurrent outbreaks of herpes simplex virus, genital or oral mucocutaneous, really slows down that herpes virus. We have added in our antiviral IVs now, for anything that's retroviral (e.g., hepatitis virus), about 500 to 600 mcg of selenium, and it has been helpful in stopping these viruses. Now, I've expanded on all these anti-viral uses at our seminar, and it's on our seminar tapes, so I'm sure you'll have Professor Taylor on in the future. I'll ask Alan to discuss the antioxidant effects and other treatments for herpes.

AG: Thanks, Jonathan. Thanks, Jeff, for having us on; it's a pleasure. The coxsackie virus study was fascinating to the extent that the viruses actually mutated. In the selenium-deficient environment, they mutated; and when the study was repeated three months later in a different mouse, they showed the identical mutation on the DNA that they had seen three months before. So, evidently there is a powerful interaction between nutritional status and the virulence of organisms, and this may extend to a lot of other areas. For example, in an area of China where the soil is very deficient in selenium, people get a condition called Keshan disease, in which they get a severe, often fatal, cardiomyopathy. It was determined that if the people are supplemented with selenium, they don't get this disease

One wonders about this relationship. We know that coxsackie virus can cause myocardial problems. We know that selenium deficiency causes coxsackie virus to become virulent and mutate and cause cardiac problems, and perhaps Keshan disease in China is due to a virulent coxsackie virus.

It brings up the exciting and broad possibility that perhaps many other diseases we attribute to infectious etiologies may, in fact, be attributable to other problems. They've shown, for example, that in the mouth, a pyridoxine-deficient environment causes cavity-producing bacteria to proliferate, whereas in the presence of adequate vitamin B6, these organisms are outcompeted, and non-cavity-producing organisms occur. It's a really exciting new area for research.

Regarding cancer, in going back through the old literature, I was aware of two studies from the 1930s on the effective treatment of cancer with selenium compounds. This was not the typical sodium selenide; they were actually fairly complex selenium molecules. But these folks had apparently been doing this for a long time and getting some reversal of cancer, and then the treatment method died out. Now we saw, a few weeks ago in *JAMA*, that there is at least a very powerful preventive effect in using a small amount of selenium for a number of different cancers.

JB: One thing I've found interesting in this emerging story about selenium and herpes is the connection to things you talked about years ago -- lysine and its use therapeutically for the treatment of herpes -- how that might relate to the nitric oxide story and to glutathione peroxidase and other selenium proteins. But this arginine conversion to nitric oxide is antagonized by increased intake of lysine; and how that relates to selenium seems as though it's tying a story together that might be very interesting in terms of understanding both the mechanism of lysine, how that ties to nitric oxide, how that ties to oxidative stress

and, ultimately, selenium and these viral mutations.

AG: It may very well be true. I think one of the things we tend to forget, though, is that arginine does have a lot of benefits in the body. For example, we can treat infertility in males using arginine, and now there are some studies that show congestive heart failure improves with arginine. So when we think lysine is good and arginine is bad, we have a tendency to go overboard. There are some studies, actually, that have shown that the combination of lysine and arginine together enhances immune function in children who get sick all the time, whereas either one alone didn't have much effect.

JB: There was also a report a month ago in *Free Radical Medicine and Biology* of a clinical human trial in which 500 mg of arginine twice daily was effective in reducing oxidative stress in diabetics, because it tends to reduce malonaldehyde and other oxidation byproducts. So I don't want to give arginine a bad name in that discussion, but it seems there's possibly some interrelationship in this whole selenium story and the arginine/lysine connection.

BIBLIOGRAPHY

1. Alfthan G, Aro A, Gey F et al. Plasma homocysteine and cardiovascular disease mortality. LANCET 1997; 349:397.
2. Brzezinski A. Melatonin in humans. N ENGL J MED 1997; 336:186-195.
3. Castillo J, Davalos A, Noya M. Progression of ischaemic stroke and excitotoxic aminoacids. LANCET 1997; 349:79-83.
4. Coudray C et al. Selenium supplementation decreases the pro-oxidant and cardiotoxicity effects of adriamycin in the rat. REDOX REPORT 1996; 2(5):323-332.
5. Faure P et al. Vitamin E improves the free radical defense system potential and insulin sensitivity of rats fed high fructose diets. J NUTR 1997; 127:103-107.
6. Garg C et al. Short-term and long-term variability of plasma homocysteine measurement. CLIN CHEM 1997; 43:(1):141-145.
7. Godfrey JC, Godfrey NJ, Novick SG. Zinc for treating the common cold: review of all clinical trials since 1984. ALTERN THER 1996;2(6):63-72.
8. Herbert V, Bigaouette J. Call for endorsement of a petition to the Food and Drug Administration to always add vitamin B12 to any folate fortification or supplement. AM J CLIN NUTR 1997; 65:572-573.
9. Jang M et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. SCIENCE 1997; 275:218-20.
10. Leiner Nutritional Science Advisory Board. Selenium study takes aim at cancer. NUTR SUPPL 1997; 2:1.
11. Liebman B. The selenium surprise. NUTR ACT HEALTHLETTER January/February 1997; 8-9.
12. Luo M, Kannar K, Wahlqvist ML, O'Brien RC. Inhibition of LDL oxidation by green tea extract. LANCET 1997; 349:360-361.
13. Salmeron J et al. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997;277(6):472-477.
14. Simon E et al. Plasma and erythrocyte vitamin E content in asymptomatic hypercholesterolemic subjects. CLIN CHEM 1997; 43(2):285-289.

15. Tomoda H et al. Possible prevention of postangioplasty restenosis by ascorbic acid. AMER J CARDIOL 1996; 78:(11):1284-1286.

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