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EVENTS

DHEA IN THE SPOTLIGHT

PART 2 OF OUR EXCLUSIVE MEETING REPORT ON DHEA AND AGING

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We continue our coverage of a major meeting entitled DHEA And Aging that was held June 18-19 in Washington DC under the auspices of the New York Academy of Sciences.

The DHEA Replacement Clinical Trial

Samuel Yen (UCSD School of Medicine, La Jolla, CA) reviewed the results of his clinical experiments with DHEA, which were believed to be the first controlled human clinical trials of DHEA replacement therapy. Dr. Yen holds a use patent for the clinical use of DHEA.



Dr. Yen reported that he had conducted 3 trials. The first was at a dose of 50 mg/day and was intended to see if markers such as IGF1 (which carries out many of the actions of growth hormone) were affected by DHEA. His second and main trial was limited to 8 men and 8 women, aged 50 or over who received 100 mg of DHEA per day. A final study was specifically directed toward measuring the immunological effects of 50 mg/day of DHEA in 65-year-old human men.

The main protocol was a placebo-controlled, double-blind crossover design in which each group was switched from the original treatment (DHEA Dr. Samuel S.C. Yen or placebo) to the opposite treatment after 3 months in the first study or after 6 months in the second study. The patients were evaluated in part by direct measurements and in part by responding to questionnaires about their feelings of well being, their libido, and the like.

CHANGES IN HORMONE LEVELS IN RESPONSE TO DHEA

Three months after giving DHEA orally at a dose of 50 mg/day, circulating DHEA levels were raised to values similar to those of young adults according to Yen.

Androstenedione, testosterone and other androgen levels in both men and women remained within physiologically normal limits, although androgens in men actually fell slightly and statistically significant increases in androstenedione, testosterone, and other androgens were found in women. Prostate serum antigen rose 60% in men and 70% in women. At a dose of 100 mg/day, DHEA rose around 6 fold to more than equal the young adult levels in both men and women.

IGF-I levels were elevated slightly at 50 mg/day and moderately (by 18% in men and by about 30% in women) at 100 mg/day of DHEA. At the same time, the binding proteins for IGF-1, which inhibit its activity, fell substantially. Although IGF-1 rose in response to DHEA, there was no correlation between IGF-1 levels and DHEA levels. Yen concluded that a DHEA dose of 50-100 mg/day is reasonable.

THERAPEUTIC EFFECTS OF DHEA REPLACEMENT THERAPY

Seventy percent of the men and 85% of the women in the first study reported an improved sense of well being while taking DHEA, as opposed to 1% and 5% of men and women, respectively, while on placebo. There was no consistent effect on libido.

At the 100 mg dosage, lean body mass rose 2% in men and 2% in women, a difference that was statistically significant when the data for both sexes were pooled. Yen interpreted this result to mean that six months of treatment with DHEA resulted in a gain of almost a kilogram of muscle in both men and women! Leg strength also rose by a net of 6% in men after subtracting out a 9% gain in strength in the control group; there was no demonstrable gain in strength for the women. Fat body mass fell 6% in men, but did not fall in women.

Dr. Yen summarized the first two studies by saying that DHEA improved psychological and physical well-being, improved the ability to cope with stress, improved physical mobility, reduced chronic joint pain, improved the quality of sleep, elevated IGF-1, elevated muscle mass, and, in men but not in women, reduced body fat and increased strength. He further stated that he personally felt the improved sense of well-being was due to the improved physical fitness and improved sleep rather than to direct modification of brain neurotransmitters by DHEA or its sulfate.

CLINICAL RESTORATION OF IMMUNE SYSTEM FUNCTION

In Yen's third study, an 18% rise in IGF-1 was again demonstrated. Natural killer cells (which fight cancer) rose in number by about a third, and their ability to lyse target cells rose by about 30-75%. The ability of both T cells (which fight cancer) and B cells (which fight bacteria) to respond to appropriate stimuli by dividing was greatly improved by DHEA. The ability to make and respond to IL-2, an important immune system hormone, was also increased dramatically.

The only negative effect seen was a 6% rise in IL-6 after 4 weeks of treatment and a 42% rise after 20 weeks of treatment. IL-6 normally rises with age, and high levels are detrimental, so a reduction in IL-6 would have been desirable. DHEA-S lowers IL-6 in animals (see below), so the rise in humans was unexpected.

Yen suggested that the positive immune response might have been caused by the rise in IGF-1, but a member of the audience noted that DHEA-sulfate (but not DHEA) can improve immune response directly (by blocking inhibition of the response by the stress hormone cortisol), not just through IGF-1.

ANECDOTAL REPORTS

A number of physicians in the audience reported that they had been giving literally thousands of their patients DHEA. After Yen's talk, for example, Dr. Jorge Flechas (Hendersonville, NC) stated that he had been using Yen's hormone replacement approach for the past 40 years! He said that giving DHEA at night is not a good idea because it keeps his patients awake. He confirmed a reduction in fibromyalgia (muscle pain) but disagreed about libido, saying that he had strong indications from his patients, especially women patients, of increased libido. He uses 50 mg/day.

Both Yen and Nestler firmly opposed such uncontrolled experimentation, and repeatedly indicated that the results of doctors who use DHEA without conducting properly controlled experiments cannot be believed. Yen did admit, however, that one of his older male patients reported increased libido on DHEA.

DR. YEN MEETS THE PRESS

After Dr. Yen's presentation, a press conference was held that was led by Dr. Yen. Dr. Nestler and Dr. Baulieu also participated. Representatives from *CBS*, *CNN*, *The Washington Post*, *Health Magazine*, and *Life Extension Magazine*, as well as many others, were present.

Dr. Yen stated that DHEA's role is to maintain healthy aging, not to prolong life, and that the latter would be bad. When asked whether people should take DHEA now, Yen said yes, that half of the people at the meeting had been taking it for 4-5 years, from what he could gather, including himself. When asked how people could get it, Nestler said that it can be obtained with a doctor's prescription but that people should not be taking it now because the studies had not been done yet, though it was his personal belief that the likelihood of significant side effects was low. When pressed by the reporters as to why he was taking it now despite the lack of large human studies, Yen backed off and said he was part of a study and did not know whether he was getting it currently or not. When asked the best dose, Yen recommended 50 mg/day or less, but Nestler objected to the question itself.

DHEA REDUCES BODY FAT

Pentti K. Siiteri (University of California at San Francisco) reported that DHEA inhibits triglyceride (blood fat) synthesis in a mouse model system by about 10%, reduces fatty acid synthesis by two-thirds, and inhibits prolactin synthesis by about 70-90% (an effect which should protect against breast cancer).

In related work, Gary Gordon (G.D. Searle, Skokie, IL) reported that DHEA at a concentration of 60-240 micromolar also powerfully inhibited the maturation of pre-adipocytes (would-be fat cells) into full-fledged fat cells in tissue culture. At the same time, according to Siiteri, DHEA causes proteins related to "fat burning" to be made in greater amounts, including carnitine acetyl-CoA transferase. This appears to be one of the most central biochemical effects of DHEA.

Perhaps the latter effect helps to make up in some way for another rather shocking finding of Siiteri's, namely, that the number of mitochondria (energy-producing units) per unit volume of cytoplasm (cell sap) fell by half and that each remaining mitochondrion was smaller in the rat liver after DHEA administration. (Perhaps this loss of mitochondrial mass is a significant but previously unknown reason why animals given DHEA lose weight. In any case, it does not seem to cause any problems.) Interestingly, Siiteri found that DHEA also raised catalase levels by 50-100%. His only negative finding was that, alas, DHEA also increased cholesterol synthesis by about 50%.

DHEA COMBATS CANCER AND ATHEROSCLEROSIS

Dr. Gary Gordon noted that men and women with high DHEA or DHEAS levels enjoy a 2 to 3 fold reduction in risk for bladder cancer compared to individuals with low DHEA/DHEAS levels. He also referred to previous studies showing that DHEA inhibits carcinogenesis, limits atherosclerosis, and has other benefits in inbred animals.

Dr. Gordon's interest began with a study by Arthur Schwartz in which high doses of DHEA (450 mg/kg instilled directly into the stomach three times a week) reduced the incidence of spontaneous cancers in rodents by over 70% by 16 months of age. DHEA also dramatically reduced the size and incidence of injury and cholesterol induced atheromas (swollen areas of the blood vessel wall), probably by inhibiting the division of smooth muscle cells in the blood vessel walls. HeLa cells are a standard human tumor cell line. DHEA inhibited the growth of HeLa cells by about 95%. Finally, Gordon also noted that in a study of Garcia's, DHEA reduced the number of sites of rodent liver cancer by half.

A SUBSTITUTE FOR DHEA



Henry Lardy (Institute for Enzyme Research, University of Wisconsin, Madison, WI) and his colleagues sought a version of DHEA that could not be converted into androgens (which could masculinize women and raise prostate serum antigen) but that would still have even greater activity than DHEA. The compounds they hit on were 7-hydroxy-DHEA and 7-oxo-DHEA, neither of which either have androgenic activity nor can be converted into androgens. Lardy fed 7-oxo-DHEA to rats for 6 days without increasing seminal vesical weight (suggesting no androgenic activity), yet it otherwise resembles DHEA in its biochemical effects and is active at one-fourth the concentration needed for DHEA activity.

Lardy and colleagues are now testing the effects of 7-oxo-DHEA and other DHEA analogs on memory, immune system function, carcinogenesis, and aging itself to see if the quest for a side-effect-free version of DHEA has been achieved. So far, they have shown that histological changes in the liver seen after feeding animals DHEA for 100 days do not appear in animals fed the analog.

Lardy believes 7-oxo-DHEA is probably the actual active form of DHEA in the body. His work is being supported by a private company with a patent on 7-oxo-DHEA.

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