

EVENTS

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continued from Exploring The Future

DHEA and Memory

Moreover, when given to old and young mice, DHEA enhances memory. Some clinical case reports suggest that it can enhance memory in younger people, and completely rejuvenate the memory of old mice. DHEA also works against known memory blocker drugs when given to mice. While these are not results found in human beings, they suggest that humans will feel similar effects.

Pregnenolone is an internal hormone closely related to DHEA and the sex hormones estrogen, the androgens and testosterone. It can occur at very high levels; experiments show that it also improves memory in rats and works against memory blocker drugs, just as does DHEA, when given to mice.

Our hormones must always remain balanced. Despite the damage it causes when too high, we also need cortisone. At proper levels, cortisone improves our sense of well being. Low cortisone shows up in eczema (an inflammatory rash) and loss of memory. Cortisone also helps our brain work by keeping glucose at the right level.

Estrogen reaches low levels some time before menopause, and Hertoghe believes women need added estrogen at that time. Deficiency causes higher cholesterol levels in the blood, making women more subject to heart and artery disease. Estrogen doses in women also improve memory. All the sex hormones occur in both sexes. Estrogen in women has a very important effect on Alzheimer's disease; women taking extra estrogen after menopause decrease their risk of Alzheimer's by as much as 50 to 60 percent.

Testosterone and the androgens (a class of hormones rather than a single hormone) have their own separate effects. Levels of androgens in women are 30 percent less than those in men. Lack of androgens causes a thinning of the myelin sheaths surrounding our major nerves, and a loss of memory.

Testosterone levels correlate with the number of nerve connections in our brains. They also tend to reduce fluency of speech. Men have an andropause like the menopause of women, with symptoms including shrunken sex organs and apparent starvation or malnutrition. Testosterone also stimulates production of the special growth hormone IGF-1 (insulin growth factor 1), and both IGF-1 and HGH (human growth hormone) decrease when testosterone levels are low. Eighty-five-year-old men have testosterone levels about 85 percent of the level of young men. Young men show daily cycles in their level of testosterone while older men do not. Hertoghe suggests that a normal level of testosterone is about 300 nanograms per liter of blood.

Thyroid hormones (a second class of hormones) also decrease in our cell nuclei as we age. This decrease comes from a fall in sensitivity to thyroid hormones. Thyroid hormone levels go down as well in Alzheimer's disease; since low thyroid levels alone can produce loss of memory and dementia, this makes the symptoms of Alzheimer's much worse.

Desperate Measures?

One of the most arresting presentations at the annual A4M conference was given by Robert White, a controversial professor of neurosurgery at Case Western Reserve University, in Cleveland, who presented a discussion of his head transplant experiments.

White, who has come under fire in some national forums for alleged cruelty to animals used in his research, believes that "body transplants" (his preferred name for what he has done) even now have a distinct medical use. For someone who is already paraplegic, but with a badly deteriorating body, a body transplant may be valid medical therapy, according to White.

White specifically limited his talk to discussion of transplants of whole heads, pointing out that isolated brains maintained artificially may help the study of brain chemistry and biochemistry.

Brains also are immunologically privileged: normal immune-system attacks on foreign tissue do not touch brains. Brain transplants thus lack one major problem of other tissue transplants. His first experiment transplanted one dog's head onto another dog. The transplanted head became conscious, doing such things as licking the experimenter's hand. Could a transplant be done such that it could replace the original head and breathe on its own? White has done this, too, by taking in more of the upper spinal cord and lower brainstem of a transplanted head. More recently he has transplanted a monkey head onto the neck (and body) of another monkey.

Since then he's heard from paraplegics, men and women, who wanted such a transplanted body because their own bodies were deteriorating. The actual surgery would probably be even easier than that done with monkeys, he opines. And he ended his talk with a question: Should this operation be performed on those wanting it?

HGH and Sleep

HGH and several other pituitary hormones also play a role in our brain. Low levels of HGH cause poorer sleep and lack of REM sleep, the kind we have when we dream. Lack of REM sleep may even decrease ability to remember. Two other pituitary hormones, LH (luteinizing hormone) and FSH (follicle-stimulating hormone) actually rise in aging. FSH causes secretion of hormones from the testes or ovaries. So far, no one has found a positive function of LH in men. A fall in the secretion of HGH, together with continued secretion of somatostatin (a pituitary hormone acting against HGH), provide another example of changes in our pituitary hormones with age. Hertoghe suggests that these changes show loss of some important regulatory process as we age.

Luke Bucci, Ph.D., of the University of Utah in Salt Lake City, discussed potential nitrocatechol stimulation of HGH production in the enhancement of brain function and prevention of premature senescence. Bucci reviewed the range of information about substances which might stimulate secretion of HGH when taken orally.

HGH itself remains quite expensive, with treatment for a year costing up to \$10,000. It cannot be taken orally (it is destroyed by the digestive system), and must be injected. If we can find some less-expensive substance we might take with our food, raising HGH levels would become simpler, and many more people could keep their HGH at younger levels. This in particular could be a means to markedly improve health in many elderly people.

The optimistic side of such searches comes from one simple observation. Even in older people with low secretion of HGH, their pituitary glands still make human growth hormone. Some unknown process only blocks its secretion rather than its creation.

Many substances will increase HGH secretion, but so far we know much less about their effectiveness, side effects, and dosage, particularly in older people. Several amino acids, for instance, definitely increase HGH in younger patients, but no one has done such tests on elderly patients.

Bucci discussed the classes of substances that increase human growth hormone secretion, including amino acids, mixtures of amino acids, dipeptides (two linked amino acids), peptides (small proteins), organic acids, some B vitamins and hormones:

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- Amino acids. Those studied consisted of L-ornithine, to which 25 percent of people responded with increased HGH secretion, plus L-glutamine, L-glycine, and L-tryptophan (also called 5-HT; which releases HGH but also causes drowsiness). L-dopa (dopamine) also releases HGH but has many side effects, some dangerous.
- Mixtures of amino acids. The mixture of ornithine and arginine worked in combination much better than either alone, and at much lower doses. Research on this combination remains in its early stages, with little known about it.
- Dipeptides. Some workers have shown arginine aspartate, or arginine pyroglutamate combined with L-lysine, will cause HGH increases. One test of the latter in 25-year-old men raised their growth hormone levels while they slept.
- Peptides. Peptides are basically small proteins, and most of those studied consist of parts of GHRH (growth hormone releasing hormone) put out by the hypothalamus. The sequence now farthest along in testing and study is GHRP6, named hexarelin by the company studying it. (Of all substances he reviews, Bucci believes hexarelin may be closest to use as a drug.) Others have tried shorter sub-sequences of HGH, but without as much effect.
Intravenous doses of cholestykinin, a hormone produced by our gall bladder, and involved in controlling our digestive system, have also increased HGH secretion; since it requires intravenous dosage, its interest for oral use is low. It still raises interesting questions about how HGH secretion works, however. Bombesin, a toxin produced by glands on the skin of some toads, increases HGH secretion, too.
- Organic acids. Several have increased HGH, though sometimes only intravenously. Bucci listed ornithine alpha-ketoglutarate, which releases HGH when given at 10 gram oral doses, but which requires much less when given intravenously.
- Hormones. Melatonin has an interesting effect in that it increases the response to the other stimulants of secretion. Melatonin at a dose of 10 mg doubles response to arginine aspartate, glutamine, glycine, and the GHRH fragments. Dopamine, the neurohormone and neurotransmitter mentioned above, also increases secretion.

DHEA and pregnenolone may also increase secretion of HGH (Bucci used the word "may" here himself. The reasons for believing that either hormone would increase HGH at present are theoretical only).

- B vitamins. The major B vitamin involved is calcium pantothenate given intravenously. A combination of two molecules of pantothenate, called pantothen, also worked.

To conclude, we have many candidates for good stimulants of HGH working in older people. Still, they remain untested these subjects, so appropriate doses and choice of one or more with minimal side effects remain unknown. The current leader is hexarelin. Yet other much less expensive substances may already exist, such as glutamine or arginine-aspartate. However, someone would have to support testing and no one has come forward to do that.

Lots of scientific evidence already suggests that vitamin E delays aging of the brain and immune system. Marguerite Kay, professor of microbiology and immunology at the University of Arizona in Phoenix, discussed her own work, which may explain how vitamin E might do this. She looked at a special antigen present in aged cells, called senescent cell antigen (SCA), and the process creating it. Basically, Kay found precursors for SCA by examining cells aged in vitro.

On membrane chromatography, its precursors showed up on band 3. They turned out to be a widely known class of proteins called the band 3 proteins. These proteins transport substances through cell membranes in all species and cells so far studied. Kay found that when band 3 proteins degrade, they produce SCA. SCA then signals our immune system to remove cells containing it in their membranes.

As cells age, their ability to transport substances across their membranes goes down, a loss critical to survival of the cell. Substances for which transport ability falls off include glucose (the basic sugar supporting many cells) and a variety of ions: Ca⁺⁺, Mg⁺⁺, Na⁺, and others (living cells maintain a different level of ions inside the cell compared to outside). Band 3 proteins show up not just in the outer cell membrane but also in those separating the Golgi bodies, the nucleus, the mitochondria, and other organelles from the rest of the cell.

As band 3 proteins themselves age, these essential transport processes break down. Not only does this cause failure of transport for ions and glucose, but also structural changes inside the cell, decreased ability to attach phosphate to the proper molecules (essential to metabolism), degradation of cell parts, and the generation of SCA mentioned above. Normally SCA then causes special antibodies to bind to the cell, leading to its destruction; in aging tissues, however, swamped by too many SCA signals, our immune system

fails to clear away degraded cells fast enough.

For some time scientists have known that lack of vitamin E accelerates many aging changes. To test whether added vitamin E might protect against cell breakdown, Kay carried out experiments with CBA/CAT female mice starting at seven months (young adult mice) and 40 months (old mice). Control mice received a constant diet containing 50 mg/kg vitamin E and no beta carotene; groups of test mice had vitamin E doses ramping up to 200 mg/kg. On measuring two antibodies to show the effect on immune system destruction of brain cells, animals receiving the highest levels of vitamin E showed the least destruction.

Bring them Back ALIVE

Peter Safar, M.D., from the University of Pittsburgh, has promoted resuscitation, in terms of cardiopulmonary resuscitation and open chest CPR for many years, and now heads the Center for Resuscitation Research at the University of Pittsburgh. The current focus is on reversibility of clinical death.

He began his talk with some general comments: he expected individual life spans to soon exceed 100 years, almost entirely because of medical measures taken against aging, not improvements in resuscitation. He did add, however, that success or failure of resuscitation in a given patient showed no relation to the age of that patient.

Current CPR methods have a major defect. Even though it's now easy to restore circulation, patients frequently revive with injured brains. Only 15 percent revive with their brains in good condition. Moreover, emergency rescue teams usually need 10 to 15 minutes to reach patients, while the current limit for revival without injury remains only 5 minutes. Safar and others, therefore, have now begun to look intensively at means to improve revival after that 5 minutes. It is, essentially, revival from clinical death.

One drug, lidoflazine, which dilates coronary arteries, improves recovery if good circulation can be restored. Epinephrine also helps. Yet Safar particularly discussed the advantage of mild hypothermia (34 degrees to 36 degrees C) to help revival. Even though mild, it produces significantly improved recovery in animal experiments. Besides reducing the brain's need for oxygen, mild hypothermia also decreases inflammation, toxicity due to excitability of the effected neurons, lactic acidosis of brain tissue, and free radical reactions.

Presently, Safar and colleagues are studying mild hypothermia plus sedation for use in disasters or hemorrhagic shock, a common cause of accidental death. Patients tolerate up to two hours of mild hypothermia. Safar also seeks ways to use current insights on resuscitation when patients cannot be brought immediately to a hospital. A kit for use in such cases would contain IV fluids, a cooling pack, a prepared drug cocktail, and means to open the chest. The drug cocktail would contain thiopental and lidocaine.

Finally, Safar repeated that prevention of age-related diseases would do far more towards longevity than any methods for resuscitation. Resuscitation had most importance for what it tells about our respect for human life.

No Megadoses Needed

Vitamin E decreased the production of SCA in other cells, too. It prevented a common age-related decline in lymphocytes, an important component of our immune system. Doses given to middle-aged mice also prevented the changes in band 3 proteins leading to SCA. Vitamin E worked as well as several other antioxidants. It was particularly interesting that megadoses of vitamin E were not needed.

Kay also said, without entering into details, that some of her experiments suggest that Alzheimer's is not just a disease of brain

cells but of the entire body. For instance, some antibodies distinguish normal band 3 proteins from those occurring in Alzheimer's disease, which has some sequences differing from normal.

Richard Caselli, M.D., discussed various drugs and hormones which may help prevent Alzheimer's, including vitamin E. He also discussed the role of the apoE gene (especially the allele apoE4) in promoting Alzheimer's disease. Genetics, vitamin E, and hormones all play a statistical role: their presence or absence makes it more (or less) likely that an individual will get Alzheimer's disease. This statistical association of vitamin E with lower rates of Alzheimer's disease supports Kay's suggestions.

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