

LE Magazine June 2002

ABSTRACTS

DHEA

Oxidative derangement in rat synaptosomes induced by hyperglycaemia: restorative effect of dehydroepiandrosterone treatment.

Central nervous system damage in diabetes is caused by both cerebral atherosclerosis and the detrimental effect of chronic hyperglycaemia on nervous tissue. Hyperglycaemia is the primer of a series of cascade reactions causing overproduction of free radicals. There is increasing evidence that these reactive molecules contribute to neuronal tissue damage. Dehydroepiandrosterone (DHEA) has been reported to possess antioxidant properties. This study evaluates the oxidative status in the synaptosomal fraction isolated from the brain of streptozotocin-treated rats and the antioxidant effect of DHEA treatment on diabetic rats. Hydroxyl radical generation, hydrogen peroxide content, and the level of the reactive oxygen species was increased ($P < 0.05$) in synaptosomes isolated from streptozotocin-treated rats. The derangement of the oxidative status was confirmed by a low level of reduced glutathione and alpha-tocopherol. DHEA treatment (4 mg per day for 3 weeks, per os) protected the synaptosomes against oxidative damage: synaptosomes from diabetic DHEA-treated rats showed a significant decrease in reactive species ($P < 0.05$) and in the formation of end products of lipid peroxidation, evaluated in terms of fluorescent chromolipid ($P < 0.01$). Moreover, DHEA treatment restored the unsaturated fatty acid content of the membrane and the reduced glutathione and alpha-tocopherol levels to normal levels and restored membrane NaK-ATPase activity close to control levels. The results demonstrate that DHEA supplementation greatly reduces oxidative damage in synaptosomes isolated from diabetic rats and suggest that this neurosteroid may participate in protecting the integrity of synaptic membranes against hyperglycaemia-induced damage.

Biochem Pharmacol 2000 Aug 1;60(3):389-95

Dehydroepiandrosterone prevents oxidative injury induced by transient ischemia/reperfusion in the brain of diabetic rats.

Both chronic hyperglycemia and ischemia/reperfusion (IR) cause an imbalance in the oxidative state of tissues. Normoglycemic and streptozotocin (STZ)-diabetic rats were subjected to bilateral carotid artery occlusion for 30 min followed by reperfusion for 60 min. Rats had either been treated with dehydroepiandrosterone (DHEA) for 7, 14 or 21 days (2 or 4 mg/day per rat) or left untreated. Oxidative state, antioxidant balance, and membrane integrity were evaluated in isolated synaptosomes. IR increased the levels of reactive species and worsened the synaptic function, affecting membrane Na/K-ATPase activity and lactate dehydrogenase release in all rats. The oxidative imbalance was much severer when transient IR was induced in STZ-diabetic rats. DHEA treatment restored H₂O₂, hydroxyl radical, and reactive oxygen species to close to control levels in normoglycemic rats and significantly reduced the level of all reactive species in STZ-diabetic rats. Moreover, DHEA treatment counteracted the detrimental effect of IR on membrane integrity and function: the increase of lactate dehydrogenase release and the drop in Na/K-ATPase activity were significantly prevented in both normoglycemic and STZ-diabetic rats. The results confirm that DHEA, an adrenal steroid that is synthesized de novo by brain neurons and astrocytes, possesses a multitargeted antioxidant effect. They also show that DHEA treatment is effective in preventing both derangement of the oxidative state and neuronal damage induced by IR in experimental diabetes.

Diabetes 2000 Nov;49(11):1924-31

Dehydroepiandrosterone suppresses elevated hepatic glucose-6-phosphatase mRNA level in C57BL/KsJ-db/db mice: comparison with troglitazone.

Dehydroepiandrosterone (DHEA) is known to improve hyperglycemia of diabetic C57BL/KsJ-db/db mice that are obese and insulin resistant. In a previous study, we reported that DHEA as well as troglitazone suppresses the elevated hepatic gluconeogenic enzymes, glucose-6-phosphatase (G6Pase) and fructose-1,6-bisphosphatase (FBPase) activities in C57BL/KsJ-db/db mice. In the present study, we evaluated the changes in mRNA of G6Pase and FBPase in db/db mice. Despite hyperinsulinemia, the G6Pase mRNA level of db/db mice was elevated as compared to their heterozygote littermate db/+m mice. In contrast, the FBPase mRNA level was not elevated in db/db mice. Administration of DHEA for two weeks significantly decreased the blood glucose level and the elevated G6Pase mRNA level in db/db mice. No significant changes were seen in the FBPase mRNA level after the administration of DHEA. Administration of troglitazone also decreased the blood glucose and G6Pase mRNA level in db/db mice although no changes were seen in the FBPase mRNA level. These results suggest that the elevation of G6Pase mRNA is important in elucidating the cause of insulin resistance, and that the G6Pase gene is at least one target for the hypoglycemic effects of DHEA as an insulin sensitizing agent in db/db mice.

Dehydroepiandrosterone protects tissues of streptozotocin-treated rats against oxidative stress.

Chronic hyperglycemia in diabetes determines the overproduction of free radicals, and evidence is increasing that these contribute to the development of diabetic complications. It has recently been reported that dehydroepiandrosterone possesses antioxidant properties; this study evaluates whether, administered daily for three weeks per os, it may provide antioxidant protection in tissues of rats with streptozotocin-induced diabetes. Lipid peroxidation was evaluated on liver, brain and kidney homogenates from diabetic animals, measuring both steady-state concentrations of thiobarbituric acid reactive substances and fluorescent chromolipids. Hyperglycemic rats had higher thiobarbituric acid reactive substances formation and fluorescent chromolipids levels than controls. Dehydroepiandrosterone-treatment (4 mg/day for 3 weeks) protected tissues against lipid peroxidation: liver, kidney and brain homogenates from dehydroepiandrosterone-treated animals showed a significant decrease of both thiobarbituric acid reactive substances and fluorescent chromolipids formation. The effect of dehydroepiandrosterone on the cellular antioxidant defenses was also investigated, as impaired antioxidant enzyme activities were considered proof of oxygen-dependent toxicity. In kidney and liver homogenates, dehydroepiandrosterone treatment restored to near-control values the cytosolic level of reduced glutathione, as well as the enzymatic activities of superoxide-dismutase, glutathione-peroxidase, catalase. In the brain, only an increase of catalase activity was evident ($p < .05$), which reverted with dehydroepiandrosterone treatment. The results demonstrate that DHEA treatment clearly reduces oxidative stress products in the tissues of streptozotocin-treated rats.

Free Radic Biol Med 1999 Jun;26(11-12):1467-74

Dehydroepiandrosterone replacement in women with adrenal insufficiency.

BACKGROUND: The physiologic role of dehydroepiandrosterone in humans is still unclear. Adrenal insufficiency leads to a deficiency of dehydroepiandrosterone; we therefore, investigated the effects of dehydroepiandrosterone replacement, in patients with adrenal insufficiency. **METHODS:** In a double-blind study, 24 women with adrenal insufficiency received in random order 50 mg of dehydroepiandrosterone orally each morning for four months and placebo daily for four months, with a one-month washout period. We measured serum steroid hormones, insulin-like growth factor I, lipids, and sex hormone-binding globulin, and we evaluated well-being and sexuality with the use of validated psychological questionnaires and visual-analogue scales, respectively. The women were assessed before treatment, after one and four months of treatment with dehydroepiandrosterone, after one and four months of placebo, and one month after the end of the second treatment period. **RESULTS:** Treatment with dehydroepiandrosterone raised the initially low serum concentrations of dehydroepiandrosterone, dehydroepiandrosterone sulfate, androstenedione, and testosterone into the normal range; serum concentrations of sex hormone-binding globulin, total cholesterol, and high-density lipoprotein cholesterol decreased significantly. Dehydroepiandrosterone significantly improved overall well-being as well as scores for depression and anxiety. For the global severity index, the mean (\pm SD) change from base line was -0.18 ± 0.29 after four months of dehydroepiandrosterone therapy, as compared with 0.03 ± 0.29 after four months of placebo ($P=0.02$). As compared with placebo, dehydroepiandrosterone significantly increased the frequency of sexual thoughts ($P=0.006$), sexual interest ($P=0.002$), and satisfaction with both mental and physical aspects of sexuality ($P=0.009$ and $P=0.02$, respectively). **CONCLUSIONS:** Dehydroepiandrosterone improves well-being and sexuality in women with adrenal insufficiency.

N Engl J Med 1999 Sep 30;341(14):1013-20

Dehydroepiandrosterone prevents lipid peroxidation and cell growth inhibition induced by high glucose concentration in cultured rat mesangial cells.

The oxidative stress induced by high glucose concentration contributes to tissue damage associated with diabetes, including renal injury. Dehydroepiandrosterone (DHEA), the major secretory product of the human adrenal gland, has been shown to possess a multi-targeted antioxidant activity which is also effective against lipid peroxidation induced by high glucose. In this study we evaluated the effect of DHEA on the growth impairment which high glucose concentration induces in cultured rat mesangial cells. Primary cultures of rat mesangial cells were grown for 10 days in media containing either normal (i.e. 5.6 mmol/l) or high (i.e. 30 mmol/l) concentrations of glucose, without or with DHEA at different concentrations. The impairment of cell growth induced by high glucose was reversed by 100 nmol/l and 500 nmol/l DHEA, which had no effect on mesangial cells cultured in media containing glucose at the normal physiological concentration (5.6 mmol/l). In high-glucose cultured mesangial cells, DHEA also attenuated the lipid peroxidation, as measured by thiobarbituric acid reactive substances (TBARS) generation and 4-hydroxynonenal (HNE) concentration, and preserved the cellular content of reduced glutathione as well as the membrane Na^+/K^+ ATPase activity. The data further support the protective effect of DHEA against oxidative damage induced by high glucose concentrations, and bring into focus its possible effectiveness in preventing chronic complications of diabetes.

J Endocrinol 2000 Aug;166(2):401-6

Effects of a single bout of exercise and exercise training on steroid levels in middle-aged type 2 diabetic men: relationship to

abdominal adipose tissue distribution and metabolic status.

Lower androgen levels have been suggested to be associated with type 2 diabetes and central obesity and are probably involved in the development of atherosclerosis. The present study investigates the effect of acute and chronic exercise on Dehydroepiandrosterone (DHEA) levels in relation to abdominal fat distribution and metabolic status in type 2 diabetes. Twenty weight-stable, middle-aged males with type 2 diabetes were enrolled in the study and participated in a submaximal (VO_2 peak) and moderate (50% VO_2 peak) exercise bout. The subjects were randomly assigned either to a trained or a control group, respectively. Physical training consisted of an 8 week program of aerobic exercise (75% VO_2 peak, 45 min), twice a week and intermittent exercise, once a week, on a bicycle ergometer. Acute exercise significantly increased DHEA and Testosterone (T) levels. Physical training increased VO_2 peak (42%, $p < 0.001$), insulin sensitivity index (KITT) (57.5%, $p < 0.02$), and basal DHEA levels (36%, $p < 0.05$), and decreased HbA1c (29%, $p < 0.001$), visceral adipose tissue (VAT) (44%, $p < 0.01$) and subcutaneous adipose tissue (SAT) levels (18%, $p < 0.01$). Body weight, BMI and insulin, T levels were not modified. Changes in DHEA levels were not correlated with changes in insulin sensitivity and abdominal fat distribution. In conclusion, exercise training favourably affects DHEA levels independently of improvements of metabolic status and abdominal fat distribution in patients with type 2 diabetes.

Diabetes Metab 2000 Dec;26(6):450-7

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ABSTRACTS

The adipose tissue metabolism: role of testosterone and dehydroepiandrosterone.

Testosterone (T) and dehydroepiandrosterone (DHEA) are fat-reducing hormones, even though they exert this effect by different mechanisms. In particular, T inhibits lipid uptake and lipoprotein-lipase (LDL) activity in adipocytes, and stimulates lipolysis by increasing the number of lipolytic beta-adrenergic receptors. An indirect sign of these effects is the decrease of adipocyte leptin production. Lastly, T inhibits differentiation of adipocyte precursor cells. Concerning DHEA, this hormone does not seem to have any of T effects; however, DHEA stimulates resting metabolic rate (RMR) and lipid oxidation, and enhances glucose disposal, by increasing the expression of GLUT-1 and GLUT-4 on fat cell plasma membrane. The insulin-like effect of DHEA would be associated to a decrease of plasma insulin concentrations and, thus, to an increase of the molar ratio between lipolytic hormones and insulin. Noteworthy, the fat-reducing effect of both T and DHEA seems to be more evident at the level of visceral adipose tissue.

Int J Obes Relat Metab Disord 2000 Jun;24 Suppl 2:S59-63

Dehydroepiandrosterone sulfate and beta-cell function: enhanced glucose-induced insulin secretion and altered gene expression in rodent pancreatic beta-cells.

Administration of dehydroepiandrosterone (DHEA), or its sulfated form (DHEAS), controls hyperglycemia in diabetic rodents without directly altering insulin sensitivity. We show that DHEAS enhanced glucose-stimulated insulin secretion when administered in vivo to rats or in vitro to beta-cell lines, without changing cellular insulin content. Insulin secretion increased from 3 days of steroid exposure in vitro, suggesting that DHEAS did not directly activate the secretory processes. DHEAS selectively increased the beta-cell mRNA expression of acyl CoA synthetase-2 and peroxisomal acyl CoA oxidase in a time-dependent manner. Although DHEAS is a peroxisomal proliferator, it did not alter the mRNA expression of peroxisomal proliferator-activated receptor (PPAR) alpha or beta, or enhance the activity of transfected PPAR alpha, beta, or gamma in vitro. Thus, DHEAS directly affected the beta-cell to enhance glucose-stimulated insulin secretion and increased the mRNA expression of specific beta-cell mitochondrial and peroxisomal lipid metabolic enzymes. This effect of DHEAS on insulin secretion may contribute to the amelioration of hyperglycemia seen in various rodent models of diabetes.

Diabetes 2000 Dec;49(12):2012-20

DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: its role during aging.

Human and some other primates are unique since their adrenals secrete large amounts of dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S), which are converted into androstenedione (4-dione) and then into potent androgens and estrogens in peripheral tissues, therefore providing autonomous intracrine control to target tissues that can adjust the formation and metabolism of active sex steroids according to local requirements. Knowledge in this area has recently made rapid progress with the elucidation of the structure of most of the tissue-specific cDNAs and genes that encode the steroidogenic enzymes responsible for the transformation of these inactive precursor steroids into androgens and/or estrogens. It is estimated that 30% to 50% of total androgens in men are synthesized in peripheral intracrine tissues from inactive adrenal precursors while, in women, peripheral estrogen formation is even more important, the best estimate being 75% before menopause and 100% after menopause. The marked reduction in the formation of DHEA-S by the adrenals during aging, especially before the age of 50 years, results in a dramatic fall in the formation of active sex steroids in peripheral target tissues, a situation which is thought to be associated with a long series of age-related decreases such as insulin resistance, obesity, osteoporosis, cardiovascular diseases, loss of muscle mass, cancer and other diseases. We have demonstrated for the first time a series of medically important beneficial effects of DHEA administered for 12 months to post-menopausal women. Most interestingly, the bone mineral density significantly increased. This relatively rapid change was associated with an increase in plasma osteocalcin, a marker of bone formation, while a decrease in bone resorption reflected by a decrease in urinary hydroxyproline excretion was observed in parallel. In addition, the estrogenic stimulation of vaginal cytology in the absence of any sign of stimulatory effect on the endometrium is also of potentially major interest for the prevention and management of menopause. Furthermore, the inhibitory effect of DHEA on the growth of human breast cancer xenografts in vivo in nude mice supports the beneficial use of DHEA as hormone replacement therapy in women.

Steroids 1998 May-Jun;63(5-6):322-8

Age-related changes of the hypothalamic-pituitary-adrenal axis: pathophysiological correlates.

The aim of this review was to examine the evidence for age-related changes of the hypothalamic-pituitary-adrenal (HPA) axis in both

physiological and pathological aging, on the basis of the many data in the literature, as well as of our personal findings. A statistically significant circadian rhythmicity of serum cortisol was maintained in elderly subjects, even if with a reduced amplitude of the 24 h fluctuations and a trend to an increase of the serum levels in the evening and at night-time, in comparison with young controls. Furthermore, an age-related impairment of HPA sensitivity to steroid feedback was present in elderly people. The occurrence of senile dementia amplified the changes already present in physiological aging. While the cortisol secretion was generally well maintained in aging, the adrenal production of dehydroepiandrosterone and of its sulfate (DHEAS) exhibited an age-related decline. Therefore, the cortisol/DHEAS molar ratio was significantly higher in elderly subjects and even more in demented ones, than in young controls. Due to the opposite effects of cortisol and DHEAS on the brain and particularly on the hippocampal region, the imbalance between glucocorticoids and androgens occurring in physiological and even more in pathological aging, may have adverse effects on the function of this region, whose key role in learning and memory is well known.

Eur J Endocrinol 2001 Apr;144(4):319-29

Effects of age on serum dehydroepiandrosterone sulfate, IGF-I, and IL-6 levels in women.

Data from animal and in vitro studies suggest that the growth-promoting effects of the adrenal androgen dehydroepiandrosterone sulfate (DHEAS) may be mediated by stimulation of insulin-like growth factor-I (IGF-I) and/or inhibition of interleukin 6 (IL-6), a cytokine mediator of bone resorption. This study tests the hypotheses that there are effects of age on serum DHEAS, IGF-I, and IL-6 levels, and that levels of IGF-I and IL-6 are related to DHEAS levels. The study included 102 women: 27 premenopausal and 75 postmenopausal, including 35 postmenopausal women with osteoporosis, as defined by bone mineral density scores by dual X-ray energy absorptiometry. DHEAS levels decreased significantly with age ($r = -0.52$, $P < 0.0001$) and IGF-I levels decreased significantly with age ($r = -0.49$, $P < 0.0001$). IL-6 levels increased significantly with age ($r = 0.36$, $P = 0.008$). IGF-I was positively correlated to DHEAS levels ($r = 0.43$, $P < 0.0001$, $n = 102$) and IL-6 levels were negatively correlated to DHEAS levels ($r = -0.32$, $P = 0.021$, $n = 54$). Levels of DHEAS and IGF-I were correlated with T scores of the spine and some hip sites. In a multiple variable model to predict DHEAS, age was an important predictor ($P < 0.001$), but osteoporosis status, IGF-I, and IL-6 were not. The median DHEAS level was lower in the postmenopausal osteoporotic women (67 microg/dl, $n = 35$) than in the nonosteoporotic postmenopausal women (106.3 microg/dl, $n = 40$, $P = 0.03$), but this was not significant after correction for age. Age accounted for 32% of the variance in DHEAS levels. In summary, DHEAS levels decreased with age and had a positive association with IGF-I levels and a negative association with IL-6 levels. DHEA deficiency may contribute.

Calcif Tissue Int 2000 Jun;66(6):414-8

Leg extensor power and dehydroepiandrosterone sulfate, insulin-like growth factor-I and testosterone in healthy active elderly people.

We examined the association between quadriceps muscle function and serum levels of dehydroepiandrosterone sulphate (DHEAS), insulin-like growth factor I (IGF-I) and testosterone in a group of healthy elderly people. Fifty-three independent, community-dwelling elderly subjects (26 men and 27 women) aged from 66 to 84 years volunteered to participate in the study. Physical activity (PA) was evaluated by a questionnaire. Quadriceps maximal muscle power (W_{max}) and optimal shortening velocity (v_{opt}) were measured on a friction-loaded non-isokinetic cycle ergometer. The W_{max} is expressed in relation to body mass ($W_{max/kg}$, $W \times kg^{-1}$), and in relation to the mass of the two quadriceps muscles ($W_{max/Quadr}$, $W \times kg(Quadr^{-1})$). In women, when adjusted for age, anthropometric measurements and PA indices, IGF-I correlated significantly with $W_{max/kg}$ (partial correlation: $r = 0.59$; $P = 0.001$), $W_{max/Quadr}$ ($r = 0.58$; $P = 0.002$) and v_{opt} ($r = 0.53$; $P = 0.004$), whereas DHEAS was correlated significantly with $W_{max/kg}$ ($r = 0.54$; $P = 0.003$) and $W_{max/Quadr}$ ($r = 0.58$; $P = 0.002$). No such correlation was found in men. These findings indicate that in healthy elderly women lower values for quadriceps muscle W_{max} and v_{opt} are related, independently of age, anthropometric measurements and PA indices, to lower circulating levels of DHEAS and IGF-I.

Eur J Appl Physiol 2000 May;82(1-2):83-90

Sexual dimorphism in the influence of advanced aging on adrenal hormone levels: the Rancho Bernardo Study.

In recent years, adrenal function and aging has been the subject of intense interest. This cross-sectional study examines age and gender differences in plasma levels of cortisol, dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEAS), and the molar ratio of cortisol/DHEAS in 50 to 89-yr-old community-dwelling adults. Plasma hormone levels were assayed in samples obtained between 0730 h and 1100 h from 857 men and 735 nonestrogen-using, postmenopausal women. Hormone levels were stratified by 10-yr age groups and compared by two-factor (gender and age) ANOVA. Overall, age and BMI-adjusted DHEA and DHEAS [collectively DHEA(S)] levels were 40% lower and cortisol levels 10% higher in women than men, resulting in a 1.7-fold higher cortisol/DHEAS molar ratio for women (both, $P < 0.001$). Cortisol levels increased progressively (20% overall) with age in both men and women (both, $P < 0.01$). Although DHEA(S) levels declined 60% and the cortisol/DHEAS ratio increased 3-fold across the 40-yr age range for both men and women (all $P < 0.001$), the pattern of the change differed (all $P < 0.01$ for interaction). For men, DHEA(S) fell in a curvilinear fashion, with the degree of change decreasing with each decade. In contrast, DHEA(S) levels in women fell 40% from the 50s to 60s, were unvarying from 60-80 years of age, and declined

an additional 18% in the 80s. The cortisol/DHEAS ratio increased in a linear fashion for men, but was flat during the 60-80-year age range for women. Despite these differences in the effect of aging, levels of DHEA(S) remained lower and cortisol and the cortisol/DHEAS ratio higher, in women than men throughout the 50-89-year age range. These results were independent of adiposity, smoking, and alcohol consumption. In summary, among older, healthy adults DHEA(S) levels are lower and cortisol levels higher in women than men. The age-related decline in adrenal androgens persists into advanced age for both men and women, but exhibits a sexually dimorphic pattern. In contrast, cortisol levels in men and women show a parallel, linear increase with aging. These findings may have important implications for a host of age-related processes that exhibit gender differences, including brain function, bone metabolism, and cardiovascular disease.

J Clin Endocrinol Metab 2000 Oct;85(10):3561-8

Effects of dehydroepiandrosterone on collagen and collagenase gene expression by skin fibroblasts in culture.

Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are the most abundant steroids in humans whose low levels are related to aging, greater incidence of various cancers, immune dysfunction, atherosclerosis and osteoporosis. It has been shown that collagen and collagenase gene expression decreases in fibroblasts taken from more aged donors. In this paper, to investigate the relationship between DHEA and skin aging, we examined the effects of DHEA on the regulation of collagen, collagenase and stromelysin-1 genes in cultured human skin fibroblasts. In collagen assay, DHEA slightly increased collagen production in a dose-related fashion, its maximal effect occurred at 10^{-5} M DHEA ($P > 0.05$). In the presence of DHEA, steady-state levels of $\alpha 1$ (I) procollagen mRNA increased to 1.6-fold of the non-treated group, while those of fibronectin were not. Interestingly, DHEA differently regulated collagenase and stromelysin-1 gene expression. The steady-state levels of collagenase mRNA decreased in response to DHEA by 40%, whereas those of stromelysin-1 mRNA increased up to 2.4-fold, compared to controls. Similar results were obtained for chloramphenicol acetyltransferase assay (CAT); maximal promoter activation of stromelysin-1 gene occurred at 10^{-6} M DHEA, 4.5-fold higher than control. CAT assay revealed that treatment with 10^{-5} M DHEA resulted in a strong (approximately 70%) inhibition of the collagenase promoter activity. In our experiments, the effects of DHEA on these gene expressions were higher at pharmacologic concentration ($\geq 10^{-5}$ M) than those at physiologic concentration (10^{-8} - 10^{-6} M). This study suggests that the level of DHEA may be related to the process of skin aging through the regulation of production and degradation in extracellular matrix.

J Dermatol Sci 2000 Jun;23(2):103-10

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ABSTRACTS

Dehydroepiandrosterone replacement administration: pharmacokinetic and pharmacodynamic studies in healthy elderly subjects.

Dehydroepiandrosterone (DHEA; 50 and 25 mg) and placebo tablets were orally administered daily to 24 healthy aging men and women (67.8 +/- 4.3 yr) for 8 days according to a balanced incomplete block design. Nine blood tests on both the first and eighth days allowed the measurement of DHEA, its sulfate DHEAS, and metabolites: testosterone, 5alpha-androstan-3alpha, 17beta-diol glucuronide, estradiol, and estrone. Relatively low background levels of DHEA(S) were observed, and with the reestablishment of "young" levels, four important results were obtained. 1) Blood DHEA had an apparent terminal half-life of more than 20 h, the same order of magnitude as that of blood DHEAS, a result explainable by back-hydrolysis of the large amount of DHEAS formed after oral administration of DHEA, a mechanism providing long-lived unconjugated DHEA and metabolites. 2) The metabolic conversion of DHEAS to DHEA was significantly greater in women than in men. 3) No accumulation of steroids was observed. 4) No worrying transformation to androgen and estrogen was recorded; indeed, the limited increased estradiol in aged women could be predicted to be beneficial. These results suggested that daily oral administration of DHEA (25/50 mg) is safe in elderly subjects. The 50-mg dose was chosen for a 1 yr, double blind, placebo-controlled trial of daily oral administration of DHEA in 60- to 80-yr-old individuals (DHEAge).

J Clin Endocrinol Metab 2000 Sep;85(9):3208-17

Chemoprevention of hormone-dependent prostate cancer in the Wistar-Unilever rat.

The high incidence and long latent period of prostate cancer make it an ideal target for chemoprevention. We have evaluated a series of agents for chemopreventive efficacy using a model in which hormone-dependent prostate cancers are induced in the Wistar-Unilever (WU) rat by sequential treatment with antiandrogen (cyproterone acetate), androgen (testosterone propionate), and direct-acting chemical carcinogen (N-methyl-N-nitrosourea), followed by chronic androgen stimulation (testosterone). This regimen reproducibly induces prostate cancers in high incidence, with no gross toxicity and a low incidence of neoplasia in the seminal vesicle and other non-target tissues. Dehydroepiandrosterone (DHEA) and 9-cis-retinoic acid (9-cis-RA) are the most active agents identified to date. DHEA inhibits prostate cancer induction both when chronic administration is begun prior to carcinogen exposure, and when administration is delayed until preneoplastic prostate lesions are present. 9-cis-RA is the most potent inhibitor of prostate carcinogenesis identified; a study to determine the efficacy of delayed administration of 9-cis-RA is in progress. Liarozole fumarate confers modest protection against prostate carcinogenesis, while N-(4-hydroxyphenyl)retinamide (fenretinide), alpha-difluoromethylornithine, oltipraz, DL-alpha-tocopherol acetate (vitamin E), and L-selenomethionine are inactive. Chemoprevention efficacy evaluations in the WU rat will support the identification of agents that merit study for prostate cancer chemoprevention in humans.

Eur Urol 1999;35(5-6):464-7

Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone.

A cross-sectional survey was made in 56 exceptionally healthy males, ranging in age from 20 to 84 years. Measurements were made of selected steroidal components and peptidic hormones in blood serum, and cognitive and physical tests were performed. Of those blood serum variables that gave highly significant negative correlations with age ($r > -0.6$), bioavailable testosterone (BT), dehydroepiandrosterone sulfate (DHEAS), and the ratio of insulin-like growth factor 1 (IGF-1) to growth hormone (GH) showed a stepwise pattern of age-related changes most closely resembling those of the age steps themselves. Of these, BT correlated best with significantly age-correlated cognitive and physical measures. Because DHEAS correlated well with BT and considerably less well than BT with the cognitive and physical measures, it seems likely that BT and/or substances to which BT gives rise in tissues play a more direct role in whatever processes are rate-limiting in the functions measured and that DHEAS relates more indirectly to these functions. The high correlation of IGF-1/GH with age, its relatively low correlation with BT, and the patterns of correlations of IGF-1/GH and BT with significantly age-correlated cognitive and physical measures suggest that the GH-IGF-1 axis and BT play independent roles in affecting these functions. Serial determinations made after oral ingestion of pregnenolone and data from the literature suggest there is interdependence of steroid metabolic systems with those operational in control of interrelations in the GH-IGF-1 axis. Longitudinal concurrent measurements of serum levels of BT, DHEAS, and IGF-1/GH together with detailed studies of their correlations with age-correlated functional measures may be useful in detecting early age-related dysregulations and may be helpful in devising ameliorative approaches.

Proc Natl Acad Sci U S A 1997 Jul 8;94(14):7537-42

Serum concentrations of estradiol and dehydroepiandrosterone sulfate and soy product intake in relation to psychological well-being in peri- and postmenopausal Japanese women.

The effect of steroid hormones, such as estrogen and dehydroepiandrosterone (DHEA) on psychological well-being of women has been suggested. Dietary estrogen may also affect psychological status. We examined the cross-sectional relationships of serum concentrations of estradiol (E2) and DHEA sulfate (DHEAS) and dietary intake of soy products to psychological status measured using the Center for Epidemiologic Studies Depression Scale (CES-D) and General Health Questionnaire (GHQ)-12 scales in 86 peri- and postmenopausal Japanese women. Intake of soy products and other dietary components was estimated from a validated semiquantitative food frequency questionnaire. A fasting blood sample was obtained from each woman to measure serum concentrations of E2 and DHEAS. Serum DHEAS was significantly inversely correlated with CES-D scale ($r = -.22$, $P = .04$) and GHQ-12 scale ($r = -.27$, $P = .01$). Soy product intake was significantly inversely correlated with CES-D scale ($r = -.22$, $P = .04$). Neither serum E2 concentration nor the ratio of serum E2 to sex hormone-binding globulin (SHBG) was associated with any of the psychological measurements. These data suggest a possibility that endogenous DHEA sulfate and dietary soy may modulate psychological well-being of peri- and postmenopausal women.

Metabolism 2000 Dec;49(12):1561-4

Dehydroepiandrosterone in the treatment of erectile dysfunction: a prospective, double-blind, randomized, placebo-controlled study.

OBJECTIVES: In 1994, the Massachusetts Male Aging Study presented an inverse correlation of the serum levels of dehydroepiandrosterone (DHEA) and the incidence of erectile dysfunction (ED). We evaluated the efficacy of DHEA replacement in the treatment of ED in a prospective, double-blind, randomized, placebo-controlled study. **METHODS:** The inclusion criteria included ED, normal physical and neurologic examinations, serum levels of testosterone, dihydrotestosterone, prolactin, and prostate-specific antigen (PSA) within the normal range, and a serum DHEA sulfate level below 1.5 micromol/L. Also all patients had a full erection after a pharmacologic erection test with 100 microg prostaglandin E1; pharmacocavernosography showed no visualization in corporeal venous structures. Forty patients from our impotence clinic were recruited and randomly divided into two groups of 20 patients each. Group 1 was treated with an oral dose of 50 mg DHEA and group 2 with a placebo one time a day for 6 months. The International Index of Erectile Function (IIEF), a 15-item questionnaire, was used to rate the success of this therapy. **RESULTS:** Therapy response was defined as the ability to achieve or maintain an erection sufficient for satisfactory sexual performance according to the National Institutes of Health Consensus Development Panel on Impotence. DHEA treatment was associated with higher mean scores for all five domains of the IIEF. There was no impact of DHEA treatment on the mean serum levels of PSA, prolactin, testosterone, the mean prostate volume, and the mean postvoid residual urine volume. **CONCLUSIONS:** Our results suggest that oral DHEA treatment may be of benefit in the treatment of ED. Although our patient data base is too small to do relevant statistical analysis, we believe that our data show a biologically obvious trend that justifies further extended studies.

Urology 1999 Mar;53(3):590-4; discussion 594-5

Effects of dehydroepiandrosterone and quinapril on nephropathy in obese Zucker rats.

BACKGROUND: The obese Zucker rat exhibits insulin resistance, develops nephropathy at an early age, and may be a model of diabetic nephropathy. Dehydroepiandrosterone (DHEA) may ameliorate many of the factors that contribute to diabetic nephropathy, while angiotensin-converting enzyme inhibitors are known to be effective. One marker of nephropathy is the expression of alpha-smooth muscle actin. **METHODS:** We studied the effect of DHEA on the expression of alpha-smooth muscle actin in obese Zucker rats and compared the changes with those in a control group, a group given quinapril, and a group on a low-calorie diet. DHEA (0.6%) added to plain chow, quinapril (0.3 mg/kg) added to drinking water, and a low-calorie diet based on pair-feeding were administered to obese rats from age 4 to 20 weeks. Immunohistochemical expression of alpha-smooth muscle actin, a marker of interstitial and glomerular fibrosis and an early indicator of nephropathy, was measured semiquantitatively in glomeruli, cortical interstitium, and medullary interstitium on a scale of 0 to 4 and was reported as mean +/- SEM. **RESULTS:** When compared with the obese control group, quinapril exhibited a marked reduction in alpha-smooth muscle actin staining in glomeruli, cortical interstitium, and medullary interstitium ($P < 0.0005$); DHEA reduced alpha-smooth muscle actin staining in cortical interstitium and medullary interstitium ($P < 0.005$), and a low-calorie diet reduced alpha-smooth muscle actin staining in cortical and medullary interstitium ($P < 0.005$), which was similar to the effects of DHEA. **CONCLUSIONS:** DHEA was similar to a low-calorie diet in reducing the immunohistochemical staining of alpha-smooth muscle actin in obese Zucker rats. However, quinapril exerted a marked protective effect on the development of fibrosis, as indicated by alpha-smooth muscle actin staining, which was significantly less than that of DHEA at the doses studied.

Kidney Int 2001 Jan;59(1):37-43

Neuroendocrine effect of a short-term treatment with DHEA in postmenopausal women.

OBJECTIVES: A progressive decline of plasma dehydroepiandrosterone (DHEA) levels occurs in women during aging related to the reduction of adrenocortical secretion. A specific action of DHEA on the central nervous system (CNS) is suggested by the

improvement of psychological and physical well-being in postmenopausal women after DHEA supplementation. The aim of the present study was to investigate the neuroendocrine effects of short-term DHEA supplementation in postmenopausal women, evaluating changes of plasma beta-endorphin (beta-EP) and growth hormone (GH) before and after oral DHEA (100 mg/day) for 7 days in postmenopausal women (n = 6). METHODS: Before and after 7 days of DHEA supplementation, postmenopausal women underwent a neuroendocrine test with clonidine, an alpha 2 presynaptic agonist for adrenergic system (1.25 mg i.v.). Basal plasma DHEA, androstenedione (A), testosterone (T), estrone (E1) and estradiol (E2) levels were evaluated before and after treatment, while plasma beta-EP and GH levels were measured before and 15, 30, 45, 60 and 90 min after clonidine injection. RESULTS: Basal plasma beta-EP and GH levels did not show a significant difference before and after short-term DHEA administration, while circulating A, T, E1 and E2 significantly increased after treatment. The clonidine test induced a significant increase of plasma beta-EP levels in women after receiving DHEA supplementation but not before; conversely, plasma GM levels increased both before and after treatment. CONCLUSIONS: The present study indicates that short-term DHEA supplementation in postmenopausal women is able to restore the impaired response of pituitary beta-EP to clonidine, an alpha 2 presynaptic agonist. According to these data it is possible to hypothesize that DHEA could play a role in the psychological and physical well-being of postmenopausal women acting via a restoration of neuroendocrine control of antero-pituitary beta-EP secretion.

Maturitas 1998 Jan 12;28(3):251-7

Dietary supplements of dehydroepiandrosterone in relation to breast cancer risk.

OBJECTIVE: Dietary supplements of the adrenocortical hormone dehydroepiandrosterone (DHEA) are widely taken in the hope of staving off the aging process. Potential dangers have not been fully researched, particularly evidence of a correlation between increased serum concentrations of DHEA and higher breast cancer risk in postmenopausal women. DESIGN: The review examines reports of clinical, epidemiological experimental studies for evidence that DHEA may be a factor in promoting the growth of mammary cancer. Biological mechanisms which might be involved are identified. RESULTS: DHEA is reported to inhibit the growth of human mammary cancer cells in vitro and also the growth of chemically-induced mammary cancer in rats. However, growth inhibition occurs only in the presence of high oestrogen concentrations, and growth stimulation occurs in both models in the presence of a low-level oestrogen milieu. Epidemiological studies report a positive correlation between higher serum concentrations of DHEA and increased breast cancer risk in the case of postmenopausal but not premenopausal women. Postulated mechanisms include a direct effect on mammary cells by androgenic metabolites of DHEA or an indirect effect by an increase in bioavailable oestrogen levels. The increased serum concentration of free insulin-like growth factor 1 which follows prolonged DHEA intake may also have a role by stimulating oestrogen receptor activity in breast tissue. CONCLUSION: Late promotion of breast cancer in postmenopausal women may be stimulated by prolonged intake of DHEA, and the risk may be increased by the endocrine abnormality associated with pre-existing abdominal obesity. Caution is advised in the use of dietary supplements of DHEA particularly by obese postmenopausal women.

Eur J Clin Nutr 1999 Oct;53(10):771-5

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ABSTRACTS

Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause.

The adrenal production of the delta 5-androgens, dehydroepiandrosterone (DHEA) and its sulfate ester dehydroepiandrosterone sulfate (DHEAS), declines linearly with aging. The evidence that DHEA or DHEAS administration may alleviate some of the problems related to aging has opened new perspectives for clinical research. The present study aims to investigate the effects of a 6-month DHEA supplementation in early and late postmenopausal women, with normal or overweight body mass index (BMI), on the level of circulating steroids, sex hormone binding globulin (SHBG), beta-endorphin and gonadotropins, and on the adrenal gland response to dexamethasone suppression and adrenocorticotrophic hormone (ACTH) stimulation. Early postmenopausal women (50-55 years) both normal weight (BMI 20-24, n = 9) and overweight (BMI 26-30, n = 9) and late postmenopausal women (60-65 years) both of normal weight and overweight, were treated with oral DHEA (50 mg/day). Circulating DHEA, DHEAS, 17-OH pregnenolone, progesterone, 17-OH progesterone, allopregnenolone, androstenedione, testosterone, dihydrotestosterone, estrone, estradiol, SHBG, cortisol, luteinizing hormone, follicle stimulating hormone and beta-endorphin levels were evaluated monthly and a Kupperman score was performed. The product/precursor ratios of adrenal steroid levels were used to assess the relative activities of the adrenal cortex enzymes. Before and after 3 and 6 months of therapy, each women underwent an ACTH stimulating test (10 micrograms i.v. in bolus) after dexamethasone administration (0.5 mg p.o.) to evaluate the response of cortisol, DHEA, DHEAS, androstenedione, 17-OH pregnenolone, allopregnanolone, progesterone and 17-OH progesterone. The between-group differences observed before treatment disappeared during DHEA administration. Levels of 17-OH pregnenolone remained constant during the 6 months. Levels of DHEA, DHEAS, androstenedione, testosterone and dihydrotestosterone increased progressively from the first month of treatment. Levels of estradiol and estrone significantly increased after the first/second month of treatment. Levels of SHBG significantly decreased from the second month of treatment only in overweight late postmenopausal women, while the other groups showed constant levels. Progesterone levels remained constant in all groups, while 17-OH progesterone levels showed a slight but significant increase in all groups. Allopregnanolone and plasma beta-endorphin levels increased progressively and significantly in the four groups, reaching values three times higher than baseline. Levels of cortisol and gonadotropins progressively decreased in all groups. The product/precursor ratios of adrenal steroid levels at the sixth month were used to assess the relative activities of the adrenal cortex enzymes and were compared to those found before therapy. The 17,20-desmolase, sulfatase and/or sulfotransferase, 17,20-lyase and 5 alpha-reductase activities significantly increased, while the 3 beta-hydroxysteroid-oxidoreductase activity did not vary. On the contrary, the 11-hydroxylase and/or 21-hydroxylase activities showed a significant decrease after 6 months of treatment. In basal conditions, dexamethasone significantly suppressed all the adrenal steroids and this suppression was greater after 3 and 6 months of treatment for DHEA, DHEAS and allopregnanolone, while it remained unchanged for other steroids. Before treatment, ACTH stimulus induced a significant response in all parameters; after the treatment, it prompted a greater response in delta 5- and delta 4-androgens, progesterone and 17-OH progesterone, while cortisol responded less in both younger and older normal-weight women. The endometrial thickness did not show significant modifications in any of the groups of postmenopausal women during the 6 months of treatment. Treatment with DHEA was associated with a progressive improvement of the Kupperman score in all groups, with major effects on the vasomotor symptoms in.

Gynecol Endocrinol 2000 Oct;14(5):342-63

Life span

Cell nonautonomy of *C. elegans* daf-2 function in the regulation of diapause and life span.

The insulin/IGF receptor homolog DAF-2 regulates the aging in *C. elegans*. Decreasing daf-2 activity causes fertile adults to remain active much longer than normal and to live more than twice as long. A more severe decrease in daf-2 function causes young larvae to enter a state of diapause rather than progressing to adulthood. We have asked which cells require daf-2 gene activity in order for the animal to develop to adulthood and to age normally. We found that daf-2 functions nonautonomously in both processes. Our findings imply that the life span of *C. elegans* is determined by a signaling cascade in which the DAF-2 receptor acts in multiple cell lineages to regulate the production or activity of a secondary signal (or signals), which, in turn, controls the growth and longevity of individual tissues in the animal.

Cell 1998 Oct 16;95(2):199-210

Regulation of life span by sensory perception in *Caenorhabditis elegans*.

Caenorhabditis elegans senses environmental signals through ciliated sensory neurons located primarily in sensory organs in the head and tail. Cilia function as sensory receptors, and mutants with defective sensory cilia have impaired sensory perception. Cilia

are membrane-bound microtubule-based structures and in *C. elegans* are only found at the dendritic endings of sensory neurons. Here we show that mutations that cause defects in sensory cilia or their support cells, or in sensory signal transduction, extend life span. Our findings imply that sensory perception regulates the life span of this animal, and suggest that in nature, its life span may be regulated by environmental cues.

Nature 1999 Dec 16;402(6763):804-9

REF-1, a protein with two bHLH domains, alters the pattern of cell fusion in *C. elegans* by regulating Hox protein activity.

Hox genes control the choice of cell fates along the anteroposterior (AP) body axis of many organisms. In *C. elegans*, two Hox genes, *lin-39* and *mab-5*, control the cell fusion decision of the 12 ventrally located Pn.p cells. Specific Pn.p cells fuse with an epidermal syncytium, *hyp7*, in a sexually dimorphic pattern. In hermaphrodites, Pn.p cells in the mid-body region remain unfused whereas in males, Pn.p cells adopt an alternating pattern of syncytial and unfused fates. The complexity of these fusion patterns arises because the activities of these two Hox proteins are regulated in a sex-specific manner. MAB-5 activity is inhibited in hermaphrodite Pn.p cells and thus MAB-5 normally only affects the male Pn.p fusion pattern. Here we identify a gene, *ref-1*, that regulates the hermaphrodite Pn.p cell fusion pattern largely by regulating MAB-5 activity in these cells. Mutation of *ref-1* also affects the fate of other epidermal cells in distinct AP body regions. *ref-1* encodes a protein with two basic helix-loop-helix domains distantly related to those of the hairy/Enhancer of split family. *ref-1*, and another hairy homolog, *lin-22*, regulate similar cell fate decisions in different body regions along the *C. elegans* AP body axis.

Development 2001 May;128(10):1793-804

The *age-1* and *daf-2* genes function in a common pathway to control the life span of *Caenorhabditis elegans*.

Recessive mutations in two genes, *daf-2* and *age-1*, extend the life span of *Caenorhabditis elegans* significantly. The *daf-2* gene also regulates formation of an alternative developmental state called the dauer. Here we asked whether these two genes function in the same or different life span pathways. We found that the longevity of both *age-1* and *daf-2* mutants requires the activities of the same two genes, *daf-16* and *daf-18*. In addition, the *daf-2(e1370); age-1(hx546)* double mutant did not live significantly longer than the *daf-2* single mutant. We also found that, like *daf-2* mutations, the *age-1(hx546)* mutation affects certain aspects of dauer formation. These findings suggest that *age-1* and *daf-2* mutations do act in the same life span pathway and extend life span by triggering similar if not identical processes.

Genetics 1995 Dec;141(4):1399-406

Genetic pathways that regulate aging in model organisms.

Searches for genes involved in the aging process have been made in genetically tractable model organisms such as yeast, the nematode *Caenorhabditis elegans*, *Drosophila melanogaster* fruitflies and mice. These genetic studies have established that ageing is indeed regulated by specific genes, and have allowed an analysis of the pathways involved, linking physiology, signal transduction and gene regulation. Intriguing similarities in the phenotypes of many of these mutants indicate that the mutations may also perturb regulatory systems that control ageing in higher organisms.

Nature 2000 Nov 9;408(6809):255-62

Signals from the reproductive system regulate the life span of *C. elegans*.

Understanding how the ageing process is regulated is a fascinating and fundamental problem in biology. Here we demonstrate that signals from the reproductive system influence the life span of the nematode *Caenorhabditis elegans*. If the cells that give rise to the germ line are killed with a laser microbeam, the life span of the animal is extended. Our findings suggest that germline signals act by modulating the activity of an insulin/IGF-1 (insulin-like growth factor) pathway that is known to regulate the aging of this organism. Mutants with reduced activity of the insulin/IGF-1-receptor homologue DAF-2 have been shown to live twice as long as normal, and their longevity requires the activity of DAF-16, a member of the forkhead/winged-helix family of transcriptional regulators. We find that, in order for germline ablation to extend life span, DAF-16 is required, as well as a putative nuclear hormone receptor, DAF-12. In addition, our findings suggest that signals from the somatic gonad also influence aging, and that this effect requires DAF-2 activity. Together, our findings imply that the *C. elegans* insulin/IGF-1 system integrates multiple signals to define the animal's rate of aging. This study demonstrates an inherent relationship between the reproductive state of this animal and its life span, and may have implications for the co-evolution of reproductive capability and longevity.

Nature 1999 May 27;399(6734):362-6

A *C. elegans* mutant that lives twice as long as wild type.

We have found that mutations in the gene *daf-2* can cause fertile, active, adult *Caenorhabditis elegans* hermaphrodites to live more than twice as long as wild type. This life span extension, the largest yet reported in any organism, requires the activity of a second gene, *daf-16*. Both genes also regulate formation of the dauer larva, a developmentally arrested larval form that is induced by crowding and starvation and is very long-lived. Our findings raise the possibility that the longevity of the dauer is not simply a consequence of its arrested growth, but instead results from a regulated life span extension mechanism that can be uncoupled from other aspects of dauer formation. *daf-2* and *daf-16* provide entry points into understanding how life span can be extended.

Nature 1993 Dec 2;366(6454):461-4

Regulation of the *Caenorhabditis elegans* longevity protein DAF-16 by insulin/IGF-1 and germline signaling.

The life span of *Caenorhabditis elegans* is regulated by the insulin/insulin-like growth factor (IGF)-1 receptor homolog DAF-2, which signals through a conserved phosphatidylinositol 3-kinase (PI 3-kinase)/Akt pathway. Mutants in this pathway remain youthful and active much longer than normal animals and can live more than twice as long. This life span extension requires DAF-16, a forkhead/winged-helix transcription factor. DAF-16 is thought to be the main target of the DAF-2 pathway. Insulin/IGF-1 signaling is thought to lead to phosphorylation of DAF-16 by AKT activity, which in turn shortens life span. Here, we show that the DAF-2 pathway prevents DAF-16 accumulation in nuclei. Disrupting Akt-consensus phosphorylation sites in DAF-16 causes nuclear accumulation in wild-type animals, but, surprisingly, has little effect on life span. Thus the DAF-2 pathway must have additional outputs. Life span in *C. elegans* can be extended by perturbing sensory neurons or germ cells. In both cases, life span extension requires DAF-16. We find that both sensory neurons and germline activity regulate DAF-16 accumulation in nuclei, but the nuclear localization patterns are different. Together these findings reveal unexpected complexity in the DAF-16-dependent pathways that regulate aging.

Nat Genet 2001 Jun;28(2):139-45

Regulation of *C. elegans* life span by insulin-like signaling in the nervous system.

An insulin-like signaling pathway controls *Caenorhabditis elegans* aging, metabolism, and development. Mutations in the *daf-2* insulin receptor-like gene or the downstream *age-1* phosphoinositide 3-kinase gene extend adult life span by two- to three-fold. To identify tissues where this pathway regulates aging and metabolism, we restored *daf-2* pathway signaling to only neurons, muscle, or intestine. Insulin-like signaling in neurons alone was sufficient to specify wild-type life span, but muscle or intestinal signaling was not. However, restoring *daf-2* pathway signaling to muscle rescued metabolic defects, thus decoupling regulation of life span and metabolism. These findings point to the nervous system as a central regulator of animal longevity.

Science 2000 Oct 6;290(5489):147-50

Patterning *C. elegans*: homeotic cluster genes, cell fates and cell migrations.

Despite its simple body form, the nematode *C. elegans* expresses homeotic cluster genes similar to those of insects and vertebrates in the patterning of many cell types and tissues along the anteroposterior axis. In the ventral nerve cord, these genes program spatial patterns of cell death, fusion, division and neurotransmitter production; in migrating cells they regulate the direction and extent of movement. Nematode development permits an analysis at the cellular level of how homeotic cluster genes interact to specify cell fates, and how cell behavior can be regulated to assemble an organism.

Trends Genet 1994 May;10(5):159-64

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