

LE Magazine March 2003

ABSTRACTS

DHEA

Dehydroepiandrosterone (DHEA)-youth hormone?

Dehydroepiandrosterone (DHEA) and its sulphated metabolite (DHEAS) are endogenous steroid hormones, synthesized by the adrenal cortex, gonads and central nervous system. The secretion profile changes with age and depends on the sex. Human DHEA and DHEAS levels decline linearly and systematically with age and suggest the potential importance of that parameter as a biomarker of aging. The counteraction of DHEA against atherosclerotic disease, cancer growth, diabetes mellitus, insulin resistance, obesity and the influence on immunological functions are observed in researches. DHEA influences the condition of mind, cognition functions, memory and well-being. DHEA hormonal replacement therapy is expected to lengthen human life by the stoppage of physiological degeneration changes and prevention of age-related clinical disorders.

Wiad Lek 2001;54(11-12):693-704

DHEA and sport.

Dehydroepiandrosterone (DHEA), a 19-carbon steroid, is situated along the steroid metabolic pathway. It is the most abundant circulating hormone in the body and can be converted to either androgens or estrogens. It is readily conjugated to its sulphate ester DHEAS, and they are designated as DHEA(S) here when used together. Its secretion reaches a peak in early adulthood and thereafter decreases, until approximately age 70 years when it reaches a concentration of approximately 20%. Many hormonal changes may take place with aging but none is as marked as this. This "relative DHEA deficiency" resulted in DHEA being enthusiastically labelled by some as a fountain of youth or an antidote to aging that would prove to be the panacea they are seeking. Its use was also taken up enthusiastically by the athletic community and used as a prohormone in the belief or hope that it would be converted mainly to testosterone in the body.

Clin J Sport Med 2002 Jul;12(4):236-41

Hippocampal perfusion and pituitary-adrenal axis in Alzheimer's disease.

The hippocampus is involved in Alzheimer's disease (AD) and regulates the hypothalamus-pituitary-adrenal axis (HPAA). Enhanced cortisol secretion has been reported in AD. Increased cortisol levels affect hippocampal neuron survival and potentiate beta-amyloid toxicity. Conversely, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS) are believed to antagonize noxious glucocorticoid effects and exert a neuroprotective activity. The present study was aimed at investigating possible correlations between hippocampus perfusion-evaluated by SPECT (Single-Photon Emission Computed Tomography)-and HPAA function in AD. Fourteen patients with AD and 12 healthy age-matched controls were studied by (99m)Tc-HMPAO high-resolution brain SPECT. Plasma adrenocorticotropin, cortisol, and DHEAS levels were determined at 2.00, 8.00, 14.00, 20.00 h in all subjects and their mean values were computed. Cortisol/DHEAS ratios (C/Dr) were also calculated. Bilateral impairment of SPECT hippocampal perfusion was observed in AD patients as compared to controls. Mean cortisol levels were significantly increased and DHEAS titers were lowered in patients with AD, as compared with controls. C/Dr was also significantly higher in patients. Using a stepwise procedure for dependent SPECT variables, the variance of hippocampal perfusional data was accounted for by mean basal DHEAS levels. Moreover, hippocampal SPECT data correlated directly with mean DHEAS levels, and inversely with C/Dr. These data show a relationship between hippocampal perfusion and HPAA function in AD. Decreased DHEAS, rather than enhanced cortisol levels, appears to be correlated with changes of hippocampal perfusion in dementia.

Neuropsychobiology 2000;42(2):51-7

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 (DHEA) stimulates neurogenesis in the hippocampus of the rat, promotes survival of newly formed neurons and prevents corticosterone-induced suppression.

Treating adult male rats with subcutaneous pellets of dehydroepiandrosterone (DHEA) increased the number of newly formed cells in the dentate gyrus of the hippocampus, and also antagonized the suppression of corticosterone (40 mg/kg body weight daily for 5 days). Neither pregnenolone (40 mg/kg/day), a precursor of DHEA, nor androstenediol (40 mg/kg/day), a major metabolite, replicated the effect of DHEA (40 mg/kg/day). Corticosterone reduced the number of cells labelled with a marker for neurons (NeuN) following a 28-day survival period, and this was also prevented by DHEA. DHEA by itself increased the number of newly formed neurons, but only if treatment was continued throughout the period of survival. Subcutaneous DHEA pellets stimulated neurogenesis in a small number of older rats (approximately 12 months old). These results show that DHEA, a steroid prominent in the blood and cerebral environment of humans, but which decreases markedly with age and during major depressive disorder, regulates neurogenesis in the hippocampus and modulates the inhibitory effect of increased corticoids on both the formation of new neurons and their survival.

Eur J Neurosci 2002 Aug;16(3):445-53

Effect of treatment of diabetic rats with dehydroepiandrosterone on vascular and neural function.

Nutritional supplementation with dehydroepiandrosterone (DHEA) may be a candidate for treating diabetes-induced vascular and neural dysfunction. DHEA is a naturally occurring adrenal androgen that has antioxidant properties and is reportedly reduced in diabetes. Using a prevention protocol, we found that dietary supplementation of streptozotocin-induced diabetic rats with 0.1, 0.25, or 0.5% DHEA caused a concentration-dependent prevention in the development of motor nerve conduction velocity and endoneurial blood flow impairment, which are decreased in diabetes. At 0.25%, DHEA significantly prevented the diabetes-induced increase in serum thiobarbituric acid-reactive substances and sciatic nerve conjugated diene levels. This treatment also reduced the production of superoxide by epineurial arterioles of the sciatic nerve. DHEA treatment (0.25%) significantly improved vascular relaxation mediated by acetylcholine in epineurial vessels of diabetic rats. Sciatic nerve Na⁺-K⁺-ATPase activity and myoinositol content was also improved by DHEA treatment, whereas sorbitol and fructose content remained elevated. These studies suggest that DHEA, by preventing oxidative stress and perhaps improving sciatic nerve Na⁺-K⁺-ATPase activity, may improve vascular and neural dysfunction in diabetes.

Am J Physiol Endocrinol Metab 2002 Nov;283(5):E1067-75

Neurosteroid quantification in human brain regions: comparison between Alzheimer's and nondemented patients.

Some neurosteroids have been shown to display beneficial effects on neuroprotection in rodents. To investigate the physiopathological significance of neurosteroids in Alzheimer's disease (AD), we compared the concentrations of pregnenolone, pregnenolone sulfate (PREGS), dehydroepiandrosterone, dehydroepiandrosterone sulfate (DHEAS), progesterone and allopregnanolone, measured by gas chromatography-mass spectrometry, in individual brain regions of AD patients and aged nondemented controls, including hippocampus, amygdala, frontal cortex, striatum, hypothalamus and cerebellum. A general trend toward decreased levels of all steroids was observed in all AD patients' brain regions compared with controls: PREGS and DHEAS were significantly lower in the striatum and cerebellum, and DHEAS was also significantly reduced in the hypothalamus. A significant negative correlation was found between the levels of cortical beta-amyloid peptides and those of PREGS in the striatum and cerebellum and between the levels of phosphorylated tau proteins and DHEAS in the hypothalamus. This study provides reference values for steroid concentrations determined by gas chromatography-mass spectrometry in various regions of the aged human brain. High levels of key proteins implicated in the formation of plaques and neurofibrillary tangles were correlated with decreased brain levels of PREGS and DHEAS, suggesting a possible neuroprotective role of these neurosteroids in AD.

J Clin Endocrinol Metab 2002 Nov;87(11):5138-43

Sex hormones and their impact on dementia and depression: a clinical perspective.

Sex hormones have often been associated with changes in behavioral and mental abilities. This paper reviews the scientific literature published between 1990 and 2000 investigating the effects of oestrogen, testosterone and dehydroepiandrosterone (DHEA) on depression and dementia. Oestrogen seems to have a positive effect in preventing, but not treating, Alzheimer's disease. Oestrogen use may also improve mood amongst women with postnatal or perimenopausal depression; however, it may contribute to increasing depressive symptoms in women with premenstrual dysphoria. The behavioural effects of testosterone and DHEA remain unclear but the results of preliminary reports suggest that their use is associated with improved mood. At present, there is not enough hard data to support the use of sex hormones and DHEA for the treatment of depression or memory deficits.

Expert Opin Pharmacother 2001 Apr;2(4):527-35

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ABSTRACTS

Medication Side Effects

Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.

OBJECTIVE: To estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospital patients. **DATA SOURCES:** Four electronic databases were searched from 1966 to 1996. **STUDY SELECTION:** Of 153, we selected 39 prospective studies from U.S. hospitals. **DATA EXTRACTION:** Data extracted independently by two investigators were analyzed by a random-effects model. To obtain the overall incidence of ADRs in hospitalized patients, we combined the incidence of ADRs occurring while in the hospital plus the incidence of ADRs causing admission to hospital. We excluded errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs. Serious ADRs were defined as those that required hospitalization, were permanently disabling, or resulted in death. **DATA SYNTHESIS:** The overall incidence of serious ADRs was 6.7% (95% confidence interval [CI], 5.2% to 8.2%) and of fatal ADRs was 0.32% (95% CI, 0.23% to 0.41%) of hospitalized patients. We estimated that in 1994 overall 2,216,000 (1,721,000-2,711,000) hospitalized patients had serious ADRs and 106,000 (76,000-137,000) had fatal ADRs, making these reactions between the fourth and sixth leading cause of death. **CONCLUSIONS:** The incidence of serious and fatal ADRs in U.S. hospitals was found to be extremely high. While our results must be viewed with circumspection because of heterogeneity among studies and small biases in the samples, these data nevertheless suggest that ADRs represent an important clinical issue.

JAMA 1998 Apr 15;279(15):1200-5

Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor.

This six-week, double-blind clinical trial evaluated lipid parameter responses to different dosages of atorvastatin in patients with primary hypercholesterolemia. Atorvastatin is a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor under development. After completing an eight-week placebo-baseline dietary phase, 81 patients were randomly assigned to receive either placebo or 2.5, 5, 10, 20, 40 or 80 mg atorvastatin once daily for six weeks. Plasma LDL cholesterol reductions from baseline were dose related, with 25% to 61% reduction from the minimum dose to the maximum dose of 80 mg atorvastatin once a day. Plasma total cholesterol and apolipoprotein B reductions were also dose related. Previously, reductions in LDL cholesterol of the magnitude observed in this study have been seen only with combination drug therapy. In this study, atorvastatin was well tolerated by hyperlipidemic patients, had an acceptable safety profile, and provided greater reduction in cholesterol than other previously reported HMG-CoA reductase inhibitors.

Arterioscler Thromb Vasc Biol 1995 May;15(5):678-82

A brief review paper of the efficacy and safety of atorvastatin in early clinical trials.

Preclinical and clinical data on atorvastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, indicate that it has superior activity in treating a variety of dyslipidemic disorders characterized by elevations in low-density lipoprotein cholesterol (LDL-C) and/or triglycerides. Results for patients randomized in early efficacy and safety studies were combined in one database and analyzed. This analysis included a total of 231 atorvastatin-treated patients (131 with hypercholesterolemia (HC), 63 with combined hyperlipidemia (CH), 36 with hypertriglyceridemia (HTG), and one with hyperchylomicronemia (Fredrickson Type V)). Patients were treated with a cholesterol-lowering diet (National Institutes of Health National Cholesterol Education Program Step 1 diet or a more rigorous diet) and either 2.5, 5, 10, 20, 40 or 80 mg/day of atorvastatin or placebo. Efficacy was based on percent change from baseline in total cholesterol, total triglycerides, LDL-C, very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), apolipoprotein B (apo B) and non-HDL-C/HDL-C. Safety was assessed in all randomized patients. Atorvastatin seemed to preferentially lower those lipid and lipoprotein component(s) most elevated within each dyslipidemic state: LDL-C in patients with HC, triglycerides and VLDL-C in patients with HTG, or all three in patients with CH. Atorvastatin was well-tolerated with a safety profile similar to other drugs in its class.

Atherosclerosis 1997 May;131(1):17-23

Adverse drug effects, compliance, and initial doses of antihypertensive drugs recommended by the Joint National Committee vs the Physicians' Desk Reference.

BACKGROUND: Compliance problems are common causes of the inadequate treatment of hypertension, with 16% to 50% of

patients quitting treatment within one year. Dose-related adverse drug events (ADEs) frequently cause compliance problems, and many ADEs occur with the initial doses of antihypertensive drugs. Thus, it is an established tenet to initiate antihypertensive therapy at low doses to avoid ADEs that diminish patients' quality of life and reduce compliance. However, what are the lowest effective doses of antihypertensive drugs? OBJECTIVE: To compare the initial doses recommended in the Physicians' Desk Reference (PDR) with those recommended by the Sixth Report of the Joint National Committee on the Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). METHODS: Review of the latest JNC VI report (1997) and the 1999 and 2000 editions of the PDR and the medical literature. RESULTS: The JNC VI recommends substantially lower initial doses for 23 (58%) of 40 drugs, compared with the PDR. In addition, for 37 (82%) of 45 drugs, PDR guidelines do not suggest lower initial doses for old or frail patients than for younger adults. CONCLUSIONS: Although the PDR is the drug reference most used by physicians, it does not reflect the lowest initial doses that are recommended by the JNC VI for many of the most prescribed antihypertensive drugs. Because avoidance of ADEs is essential to maintaining compliance with antihypertensive therapy, and because many antihypertensive ADEs are dose related, physicians must know the very lowest, effective, least ADE-prone doses. Patients and physicians would benefit by establishing mechanisms to make this information readily available to all practicing physicians.

Arch Intern Med 2001 Mar 26;161(6):880-5

Menopausal hormone replacement therapy and risk of ovarian cancer.

CONTEXT: The association between menopausal hormone replacement therapy and ovarian cancer is unclear. OBJECTIVE: To determine whether hormone replacement therapy using estrogen only, estrogen-progestin only, or both estrogen only and estrogen-progestin increases ovarian cancer risk. DESIGN: A 1979-1998 cohort study of former participants in the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. SETTING: Twenty-nine U.S. clinical centers. PARTICIPANTS: A total of 44 241 postmenopausal women (mean age at start of follow-up, 56.6 years). MAIN OUTCOME MEASURE: Incident ovarian cancer. RESULTS: We identified 329 women who developed ovarian cancer during follow-up. In time-dependent analyses adjusted for age, menopause type, and oral contraceptive use, ever use of estrogen only was significantly associated with ovarian cancer (rate ratio [RR], 1.6; 95% confidence interval [CI], 1.2-2.0). Increasing duration of estrogen-only use was significantly associated with ovarian cancer: RRs for 10 to 19 years and 20 or more years were 1.8 (95% CI, 1.1-3.0) and 3.2 (95% CI, 1.7-5.7), respectively (P value for trend <.001), and we observed a 7% (95% CI, 2%-13%) increase in RR per year of use. We observed significantly elevated RRs with increasing duration of estrogen-only use across all strata of other ovarian cancer risk factors, including women with hysterectomy. The RR for estrogen-progestin use after prior estrogen-only use was 1.5 (95% CI, 0.91-2.4), but the RR for estrogen-progestin-only use was 1.1 (95% CI, 0.64-1.7). The RRs for less than two years and two or more years of estrogen-progestin-only use were 1.6 (95% CI, 0.78-3.3) and 0.80 (95% CI, 0.35-1.8), respectively, and there was no evidence of a duration response (P value for trend =.30). CONCLUSION: Women who used estrogen-only replacement therapy, particularly for 10 or more years, were at significantly increased risk of ovarian cancer in this study. Women who used short-term estrogen-progestin-only replacement therapy were not at increased risk, but risk associated with short-term and longer-term estrogen-progestin replacement therapy warrants further investigation.

JAMA 2002 Jul 17;288(3):334-41

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ABSTRACTS

Creatine

Creatine monohydrate in muscular dystrophies: A double-blind, placebo-controlled clinical study.

The authors assessed the safety and efficacy of creatine monohydrate (Cr) in various types of muscular dystrophies in a double-blind, crossover trial. Thirty-six patients (12 patients with facioscapulohumeral dystrophy, 10 patients with Becker dystrophy, eight patients with Duchenne dystrophy and six patients with sarcoglycan-deficient limb girdle muscular dystrophy) were randomized to receive Cr or placebo for eight weeks. There was mild but significant improvement in muscle strength and daily-life activities by Medical Research Council scales and the Neuromuscular Symptom Score. Cr was well tolerated throughout the study period.

Neurology 2000 May 9;54(9):1848-50

Creatine monohydrate increases strength in patients with neuromuscular disease.

Creatine monohydrate has been shown to increase strength in studies of young healthy subjects and in a few studies with patients. Creatine monohydrate (10 g daily for five days to 5 g daily for five days) was administered to patients with neuromuscular disease in a pilot study (Study 1; n = 81), followed by a single-blinded study (Study 2; n = 21). Body weight, handgrip, dorsiflexion, and knee extensor strength were measured before and after treatment. Creatine administration increased all measured indices in both studies. Short-term creatine monohydrate increased high-intensity strength significantly in patients with neuromuscular disease.

Neurology 1999 Mar 10;52(4):854-7

Neuroprotective effects of creatine administration against NMDA and malonate toxicity.

We examined whether creatine administration could exert neuroprotective effects against excitotoxicity mediated by N-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainic acid. Oral administration of 1% creatine significantly attenuated striatal excitotoxic lesions produced by NMDA, but had no effect on lesions produced by AMPA or kainic acid. Both creatine and nicotinamide can exert significant protective effects against malonate-induced striatal lesions. We, therefore, examined whether nicotinamide could exert additive neuroprotective effects with creatine against malonate-induced lesions. Nicotinamide with creatine produced significantly better neuroprotection than creatine alone against malonate-induced lesions. Creatine can, therefore, produce significant neuroprotective effects against NMDA mediated excitotoxic lesions in vivo and the combination of nicotinamide with creatine exerts additive neuroprotective effects.

Brain Res 2000 Mar 31;860(1-2):195-8

Creatine and cyclocreatine attenuate MPTP neurotoxicity.

Systemic administration of 1-methyl-4-phenyl-1,2,3, 6-tetrahydropyridine (MPTP) produces parkinsonism in experimental animals by a mechanism involving impaired energy production. MPTP is converted by monoamine oxidase B to 1-methyl-4-phenylpyridinium (MPP⁺), which blocks complex I of the electron transport chain. Oral supplementation with creatine or cyclocreatine, which are substrates for creatine kinase, may increase phosphocreatine (PCr) or cyclophosphocreatine (PCCr) and buffer against ATP depletion and thereby exert neuroprotective effects. In the present study we found that oral supplementation with either creatine or cyclocreatine produced significant protection against MPTP-induced dopamine depletions in mice. Creatine protected against MPTP-induced loss of Nissl (granular endoplasmic reticulum and ribosomes) and tyrosine hydroxylase immunostained neurons in the substantia nigra. Creatine and cyclocreatine had no effects on the conversion of MPTP to MPP⁺ in vivo. These results further implicate metabolic dysfunction in MPTP neurotoxicity and suggest a novel therapeutic approach, which may have applicability for Parkinson's disease.

Exp Neurol 1999 May;157(1):142-9

Role of creatine and phosphocreatine in neuronal protection from anoxic and ischemic damage.

Phosphocreatine can to some extent compensate for the lack of ATP (Adenosine Triphosphate) synthesis that is caused in the brain by deprivation of oxygen or glucose. Treatment of in vitro rat hippocampal slices with creatine increases the neuronal store of phosphocreatine. In this way it increases the resistance of the tissue to anoxic or ischemic damage. In vitro brain slices

pretreatment with creatine delays anoxic depolarization (AD) and prevents loss of evoked potentials that is caused by transient anoxia, although it seems so far not to be active against milder, not AD-mediated, damage. Although creatine crosses the blood-brain barrier poorly, its administration in vivo at high doses through the intracerebroventricular or the intraperitoneal way causes an increase of cerebral phosphocreatine that has been shown to be of therapeutic value in vitro. Accordingly, preliminary data show that creatine pretreatment decreases ischemic damage in vivo.

Amino Acids 2002;23(1-3):221-9

Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's disease.

The gene defect in Huntington's disease (HD) may result in an impairment of energy metabolism. Malonate and 3-nitropropionic acid (3-NP) are inhibitors of succinate dehydrogenase that produce energy depletion and lesions that closely resemble those of HD. Oral supplementation with creatine or cyclocreatine, which are substrates for the enzyme creatine kinase, may increase phosphocreatine (PCr) or phosphocyclocreatine (PCCr) levels and ATP generation and thereby may exert neuroprotective effects. We found that oral supplementation with either creatine or cyclocreatine produced significant protection against malonate lesions, and that creatine but not cyclocreatine supplementation significantly protected against 3-NP neurotoxicity. Creatine and cyclocreatine increased brain concentrations of PCr and PCCr, respectively, and creatine protected against depletions of PCr and ATP produced by 3-NP. Creatine supplementation protected against 3-NP induced increases in striatal lactate concentrations in vivo as assessed by ¹H magnetic resonance spectroscopy. Creatine and cyclocreatine protected against malonate-induced increases in the conversion of salicylate to 2,3- and 2,5-dihydroxybenzoic acid, biochemical markers of hydroxyl radical generation. Creatine administration protected against 3-NP-induced increases in 3-nitrotyrosine concentrations, a marker of peroxynitrite-mediated oxidative injury. Oral supplementation with creatine or cyclocreatine results in neuroprotective effects in vivo, which may represent a novel therapeutic strategy for HD and other neurodegenerative diseases.

J Neurosci 1998 Jan 1;18(1):156-63

Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease.

Huntington's disease (HD) is a progressive neurodegenerative illness for which there is no effective therapy. We examined whether creatine, which may exert neuroprotective effects by increasing phosphocreatine levels or by stabilizing the mitochondrial permeability transition, has beneficial effects in a transgenic mouse model of HD (line 6/2). Dietary creatine supplementation significantly improved survival, slowed the development of brain atrophy, and delayed atrophy of striatal neurons and the formation of huntingtin-positive aggregates in R6/2 mice. Body weight and motor performance on the rotarod test were significantly improved in creatine-supplemented R6/2 mice, whereas the onset of diabetes was markedly delayed. Nuclear magnetic resonance spectroscopy showed that creatine supplementation significantly increased brain creatine concentrations and delayed decreases in N-acetylaspartate concentrations. These results support a role of metabolic dysfunction in a transgenic mouse model of HD and suggest a novel therapeutic strategy to slow the pathological process.

J Neurosci 2000 Jun 15;20(12):4389-97

Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis.

Mitochondria are particularly vulnerable to oxidative stress, and mitochondrial swelling and vacuolization are among the earliest pathologic features found in two strains of transgenic amyotrophic lateral sclerosis (ALS) mice with SOD1 mutations. Mice with the G93A human SOD1 mutation have altered electron transport enzymes, and expression of the mutant enzyme in vitro results in a loss of mitochondrial membrane potential and elevated cytosolic calcium concentration. Mitochondrial dysfunction may lead to ATP depletion, which may contribute to cell death. If this is true, then buffering intracellular energy levels could exert neuroprotective effects. Creatine kinase and its substrates creatine and phosphocreatine constitute an intricate cellular energy buffering and transport system connecting sites of energy production (mitochondria) with sites of energy consumption, and creatine administration stabilizes the mitochondrial creatine kinase and inhibits opening of the mitochondrial transition pore. We found that oral administration of creatine produced a dose-dependent improvement in motor performance and extended survival in G93A transgenic mice, and it protected mice from loss of both motor neurons and substantia nigra neurons at 120 days of age. Creatine administration protected G93A transgenic mice from increases in biochemical indices of oxidative damage. Therefore, creatine administration may be a new therapeutic strategy for ALS.

Nat Med 1999 Mar;5(3):347-50

Creatine supplementation in chronic heart failure increases skeletal muscle creatine phosphate and muscle performance.

BACKGROUND: Cardiac creatine levels are depressed in chronic heart failure. Oral supplementation of creatine to healthy volunteers has been shown to increase physical performance. **AIM:** To evaluate the effects of creatine supplementation on ejection fraction, symptom-limited physical endurance and skeletal muscle strength in patients with chronic heart failure. **METHODS:** With a

double-blind, placebo-controlled design 17 patients (age 43 to 70 years, ejection fraction < 40) were supplemented with creatine 20 g daily for 10 days. Before and on the last day of supplementation ejection fraction was determined by radionuclide angiography as was symptom-limited 1-legged knee extensor and 2-legged exercise performance on the cycle ergometer. Muscle strength as unilateral concentric knee extensor performance (peak torque, Nm at 180 degrees/s) was also evaluated. Skeletal muscle biopsies were taken for the determination of energy-rich phosphagens. RESULTS: Ejection fraction at rest and at work did not change. Performance before creatine supplementation did not differ between placebo and creatine groups. While no change was seen in the placebo group compared to baseline, creatine supplementation increased skeletal muscle total creatine and creatine phosphate by 17 +/- 4% (P < 0.05) and 12 +/- 4% (P < 0.05), respectively. Increments were seen only in patients with < 140 mmol total creatine/kg d.w. (P < 0.05). One-legged performance (21%, P < 0.05), 2-legged performance (10%, P < 0.05), and peak torque, Nm (5%, P < 0.05) increased. Both peak torque and 1-legged performance increased linearly with increased skeletal muscle phosphocreatine (P < 0.05). The increments in 1-legged, 2-legged and peak torque were significant compared to the placebo group, (P < 0.05). CONCLUSIONS: One week of creatine supplementation to patients with chronic heart failure did not increase ejection fraction but increased skeletal muscle energy-rich phosphagens and performance as regards both strength and endurance. This new therapeutic approach merits further attention.

Cardiovasc Res 1995 Sep;30(3):413-8

The effect of dietary creatine supplementation on skeletal muscle metabolism in congestive heart failure.

AIMS: To assess the effects of dietary creatine supplementation on skeletal muscle metabolism and endurance in patients with chronic heart failure. METHODS: A forearm model of muscle metabolism was used, with a cannula inserted retrogradely into an antecubital vein of the dominant forearm. Maximum voluntary contraction was measured using handgrip dynamometry. Subjects performed handgrip exercise, 5-s contraction followed by 5-s rest for five min at 25%, 50%, and 75% of maximum voluntary contraction or until exhaustion. Blood was taken at rest and zero and two minutes after exercise for measurement of lactate and ammonia. After 30 minutes the procedure was repeated with fixed workloads of 7 kg, 14 kg and 21 kg. Patients were assigned to creatine 20 g daily or matching placebo for five days and returned after six days for repeat study. RESULTS: Contractions (median (25th, 75th interquartiles)) until exhaustion at 75% of maximum voluntary contraction increased after creatine treatment (8 (6, 14) vs 14 (8, 17), P = 0.025) with no significant placebo effect. Ammonia per contraction at 75% maximum voluntary contraction (11.6 mmol/l/contraction (8.3, 15.7) vs 8.9 mmol/l/contraction (5.9, 10.8), P = 0.037) and lactate per contraction at 75% maximum voluntary contraction (0.32 mmol/l/contraction (0.28, 0.61) vs 0.27 mmol/l/contraction (0.19, 0.49), P = 0.07) fell after creatine but not after placebo. CONCLUSIONS: Creatine supplementation in chronic heart failure augments skeletal muscle endurance and attenuates the abnormal skeletal muscle metabolic response to exercise.

Eur Heart J 1998 Apr;19(4):617-22

Nutritional assessment and muscle energy metabolism in severe chronic congestive heart failure-effects of long-term dietary supplementation.

In order to investigate nutritional status in relation to the metabolic state of skeletal muscle in patients with severe congestive heart failure, and to explore the influence of long-term dietary supplementation, 22 patients were randomized in a double-blind study to receive either a placebo (n = 13) or high caloric fluid (n = 9). Before treatment, the muscle content of adenosine triphosphate (ATP), creatine and glycogen was lower than in healthy individuals, and muscle biopsies revealed an excess of water. Two patients were found to be malnourished according to nutritional assessment criteria. Following study treatment, no significant changes occurred, either within or between the two subgroups. Thus, patients with severe congestive heart failure displayed metabolic derangement in skeletal muscle which did not seem to be explained by malnutrition.

Eur Heart J 1994 Dec;15(12):1641-50

Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia.

OBJECTIVE: To investigate the metabolic and functional status of muscles of fibromyalgia (FM) patients, using P-31 magnetic resonance spectroscopy (MRS). METHODS: Twelve patients with FM and 11 healthy subjects were studied. Clinical status was assessed by questionnaire. Biochemical status of muscle was evaluated with P-31 MRS by determining concentrations of inorganic phosphate (Pi), phosphocreatine (PCr), ATP, and phosphodiesteres during rest and exercise. Functional status was evaluated from the PCr/Pi ratio, phosphorylation potential (PP), and total oxidative capacity (Vmax). RESULTS: Patients with FM reported greater difficulty in performing activities of daily living as well as increased pain, fatigue, and weakness compared with controls. MRS measurements showed that patients had significantly lower than normal PCr and ATP levels (P < 0.004) and PCr/Pi ratios (P < 0.04) in the quadriceps muscles during rest. Values for PP and Vmax also were significantly reduced during rest and exercise. CONCLUSION: P-31 MRS provides objective evidence for metabolic abnormalities consistent with weakness and fatigue in patients with FM. Noninvasive P-31 MRS may be useful in assessing clinical status and evaluating the effectiveness of treatment regimens in FM.

High-performance capillary electrophoresis-pure creatine monohydrate reduces blood lipids in men and women.

1. A randomized, double-blind, placebo-controlled trial utilizing creatine as a potential lipid-lowering agent was conducted to determine plasma lipid, lipoprotein, glucose, urea nitrogen and creatinine profiles in men and women ranging in age from 32 to 70 years. 2. Thirty-four subjects (18 men and 16 women) with total cholesterol concentrations exceeding 200 mg/dl received either a creatine supplement (5 g of creatine plus 1 g of glucose) or a glucose placebo (6 g of glucose) for 56 days. Creatine and placebo were taken orally four times a day for five days and then twice a day for 51 days. Plasma analyses were measured at baseline, four and eight weeks of treatment, and at four weeks after cessation of treatment (week 12). 3. Significant reductions in plasma total cholesterol, triacylglycerols and very-low-density lipoprotein-C occurred within the creatine monohydrate group. Minor reductions in plasma total cholesterol from baseline (233 +/- 9 mg/dl) of 6% and 5% occurred at weeks four and eight, respectively, before returning to baseline at week 12. Baseline triacylglycerols (194 +/- 21 mg/dl) and very-low-density lipoprotein-C (39 +/- 4 mg/dl) were reduced by 23% and 22% at weeks four and eight, respectively, and remained attenuated by 26% at week 12. These results remained consistent when data were separated and analysed by gender. Finally, a small, but statistically significant increase in urea nitrogen was observed in women between baseline (11.8 +/- 0.7 mg/dl) and week eight (13.8 +/- 0.7 mg/dl, $P < 0.05$). No significant differences were noted for low-density lipoprotein-C, high-density lipoprotein-C, total cholesterol/high-density lipoprotein ratio, glucose, creatinine, body mass, body mass index or physical activity within or between the experimental and placebo groups. However, a trend towards reduced blood glucose levels was present in males given creatine monohydrate ($P = 0.051$). 4. These preliminary data suggest that creatine monohydrate may modulate lipid metabolism in certain individuals. These observations may demonstrate practical efficacy to the hyperlipidemic patient as well as providing possible new mechanistic insights into the cellular regulation of blood lipid concentrations.

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Effect of oral creatine supplementation on muscle [PCr] and short-term maximum power output.

Our purpose was to determine the effect of creatine supplementation on power output during a 30-s maximal cycling (Wingate) test. Nine males underwent three randomly ordered tests following ingestion of a creatine supplementation (CRE), placebo (PLA), and control (CON). CRE was ingested as creatine monohydrate (CrH₂O) dissolved in a flavored drink (20g.d⁻¹ for 3 d), while PLA consisted of the drink only. Tests were performed 14 d apart on a Monarch ergometer modified for immediate resistance loading. Needle biopsies were taken from the vastus lateralis at the end of each treatment period and before the exercise test. No difference was found between conditions for peak, mean 10-s, and mean 30-s power output, percent fatigue, or post-exercise blood lactate concentration. Similarly, no difference between conditions was observed for ATP, phosphocreatine (PCr), or total creatine (TCr); however, the TCr/ATP was higher in the CRE condition ($P < 0.05$) than in the CON and PLA conditions. Findings suggest that 3 d of oral Cr supplementation does not increase resting muscle PCr concentration and has no effect on performance during a single short-term maximal cycling task.

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