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Stabilized NADH improves the physical and mental performance in highly conditioned athletes

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Summary

In 1995 a study was conducted among competitive-level cyclists and long distance runners taking ENADA/NADH. A significant range of performance improvements was recorded such as increased oxygen capacity, decreased reaction time and greater mental acuity. Based on these results a double blind, placebo-controlled cross-over study was organized at the Department of Sports Medicine of the University Clinic in Freiburg, Germany with the new sublingual NADH formulation (ENADAlert) with highly conditioned athletes who were given 30 mg tablets ENADAlert for one month. Their performance was measured by spiroergometry at baseline and after the one month treatment period. Fourteen athletes (18 to 49 years, VO_2 max, 55 ml x kg^{-1} x min^{-1}) were tested. Placebo or ENADAlert (30mg/day) was given for four weeks. After a six weeks wash-out period, subjects of the placebo group received ENADAlert and the ENADAlert group received placebo. The performance tests were done at the beginning and after the intervention phase always with two examinations before and after the cross-over. The max. aerobic capacity was determined. Side effects, changes in the safety parameters (liver, kidney and other blood values) have not been observed. No drop-outs did occur. The following changes are attributed to a positive treatment effect: (1) reduction of oxygen consumption, (2) increase in respiratory coefficient RQ at defined work-out, (3) reduction of CO_2 exhalation and (4) reduction of lactate levels. If you correlate the individual values for VCO_2 and VO_2 per breath stroke in a scattergram, one can calculate a certified treatment effect of seven percent more muscular energy after ENADAlert™. The reduction of the oxygen consumption and the shift in the CO_2/O_2 scattergram under the influence of NADH indicate an improved cellular oxygen utilization. The additional gain in energy supply is most likely due to an increased ATP-supply. ENADAlert™, the stabilized sublingually absorbed NADH formulation can increase muscular energy supply in highly conditioned athletes by an average of 7%. The decrease in lactate

level after intake of NADH implies that athletes can perform longer under aerobic physiological conditions.

Introduction

NADH (nicotinamide adenine dinucleotide hydride) is one of the most important coenzymes present in every living cell. NADH catalyzes more than thousand metabolic reactions the most important of which is the trigger for ATP production[1]. Furthermore, it plays a decisive role in cell regulation and DNA repair[2] as well as stimulator of the cellular immune system.[3] Due to his high redox potential, NADH has an enormous antioxidative capacity[4]. The content of NADH in organ and tissue reflects the need for it. The highest concentration is found in heart cells (90 mcg/g tissue), brain (50 mcg/g tissue) and muscles (50 mcg/g tissue). The organs with the highest amount for energy (heart and brain) contain the highest level of NADH. In an aging organism and in any patient with chronic diseases a certain NADH deficiency[5] and ATP deficiency[6] could be detected. This leads to a decline in the availability of energy of the cells and organs. *In vitro* as well as *in vivo* studies showed that the cellular energy metabolism and ATP production can be improved by exogenous NADH[7,8]. Based on this finding, a study protocol was developed to find out whether the stabilized, orally absorbable form of NADH (ENADAlert) has an energy and performance increase effect.

Method

In a double-blind, placebo-controlled cross-over study, fourteen highly conditioned athletes (18-49 yrs, VO_2 max > 55 ml/kg/min) with a constant training and nutritional program were investigated. They received ENADAlert (sublingual form of NADH) or an identically looking placebo tablet. The daily dosage was 30 mg of NADH which was applied for four weeks. After that, a six-week wash-out phase took place and then, in a cross-over design the placebo subject received NADH and the NADH subject received placebo. The maximal aerobic capacity was determined on a tread mill including spiroergometry. As parameter for

ventilation, the oxygen uptake (VO_2 in ml/min) and the carbon dioxide exhalation (VCO_2 in ml/min) were measured. In addition, the heart frequency as well as the lactate levels in capillary blood was determined. The respiratory ratio (RQ) was calculated. The subjects were examined in a standard tread mill with a long-term endurance test in which a steady state at 7% of the individual VO_2 max over 14 minutes to place. For the entire test period, the parameters for ventilation VO_2 and VCO_2 were determined. The data of the cross-over design were evaluated by non-parametric statistical procedures (Mann-Whitney-Wilcoxson-test). Approbability of $P < 0.05$ was regarded as statistical significant.

Results

Subjects received 30 mg/day over a period of four weeks. Neither side-effects nor changes in all clinical chemical and hematological parameters were observed. No drop-outs did occur. Changes in the training condition or well-being have not been found in the diary. Under NADH, a reduced uptake of oxygen of 6.2% (base is 0.07; 42.8 vs. 40.2 ml/kg/min) could ascertain this treatment effect. This reduction of oxygen consumption could also be found by using the RQ in the aerobic transition phase (VO_2 values around 3000 ml). If the individual values for VCO_2 and VO_2 per breath stroke are inserted in a scattergram and evaluated, a coefficient could be calculated which differs in the subjects taking NADH, than in the subjects taking placebo. An O_2 sparring effect of 5.9% was found under supplementation with NADH. The heart frequency and lactate level in the blood were identical between the placebo and the NADH group. However, in the endurance trial under aerobic steady state condition, a 14% lower lactate level was found in the NADH group. ($p = 0.07$, 1.67 vs. 1.43 mmol/l). The additional gain in energy supply is most likely due to an increase of the ATP production. ENADAlert™, the stabilized, sublingually absorbed form of NADH can increase muscular

energy in athletes by an average of 7%.[7] The decrease in lactate levels after intake of NADH implies that athletes can perform longer under aerobic physiological conditions.

Discussion

In vitro studies have shown that NADH does influence the metabolism of a cell, in particular the production of NADH. In a double-blind, placebo-controlled, FDA approved clinical trial it has been demonstrated that ENADA/NADH can improve the energy level of subjects suffering from chronic fatigue syndrome (CFS)[9]. In another study, it was found that patients suffering from chronic fatigue syndrome do show an ATP deficiency in their muscle tissue after physical exercise as measured by nuclear magnetic resonance[6]. The question this study has answered was: Can highly conditioned athletes, from whom one would assume that they have a maximum reserve in energy, still gain an increase? In order to achieve this, NADH must enter the cell and must reach the target in the cell where ATP is produced. ENADA, the stabilized, orally absorbable form of NADH, is absorbed in the intestinal tract. NADH penetrates the intestinal mucosa by passive diffusion. ENADA also passes the blood-brain-barrier as shown by studies performed in rats. 20 minutes after oral application of ENADA/NADH to rats, an increase of NADH in the rat brain court was detected by laser induced NADH fluorescence[10]. There is also evidence that NADH must penetrate the cell membrane and possibly also the mitochondrial membrane. When pheochromacytoma cells (PC12 cells) are incubated with NADH in the culture medium, an increase in mitochondrial membrane potential can be detected[11]. This finding provides indirect evidence of a higher energetic state of the cell. Even more convincing evidence could be obtained in isolated single heart cells. If these cells are incubated with NADH, a dosage-dependent increase in ATP concentration in the cell can be found[12]. From this observation one can deduce that NADH must pass the cell membrane to induce ATP production. This is the most likely mechanism by which ENADA/NADH leads to an increase in energy state in muscle tissue.

The reduction of the oxygen consumption and a change in the CO_2/O_2 scattergram indicates an improved cellular bioavailability of NADH and due to this to an increased ATP supply. This mechanism of action is supported by the reduction of the lactate level in the blood under NADH treatment. If highly conditioned athletes gain on average 7% more muscular energy by NADH, one can calculated on the basis of well-known parameters that healthy non-athletic individuals may achieve a gain in energy of 25%. As a constant decline in energy production is observed in elderly people, the energy level of these individuals could be increased considerably by supplementing with ENADA/NADH. Finally, an application in the field of so-called mitochondrial diseases such as Parkinson's and Alzheimer's disease could be considered. In those ailments, the energy production in the mitochondria is disturbed and reduced. In a number of controlled clinical trials it could be shown that ENADA improves symptoms of patients with Parkinson's disease and Alzheimer's disease. Therefore ENADA, the stabilized, orally absorbable form of NADH may be helpful for a number of bioenergetic related ailments.

References

1. Alberts B., Bray D., Lewis J., Raff M., Roberts K., Watson J.D.: Energy Conversion: Mitochondria and chloroplasts. In: Molecular biology of the cell. 3rd ed. New York: Garland; 1994.
2. Zhang J.R., Vrecko K., Nadlinger K., Storga-Tomic D., Birkmayer G.D., Reibnegger G.: The reduced coenzyme nicotinamide dinucleotide (NADH) repairs DNA damage of PC12 cells induced by doxorubicin. J Tumor Marker Oncol 1998; 13:5-17.
3. Nadlinger K., Birkmayer J. Gebauer F and Kunze R.: Influence of Reduced Nicotinamide Adenine Dinucleotide on the Production of Interleukin-6 by Peripheral Human Blood Leukocytes. Neuroimmunomodulation 2002; in press

4. 4.Stryer L.: Oxidative Phosphorylation. In: Stryer L., editor. Biochemistry. 3rd ed. San Francisco and New York: W.H. Freeman and Co.; 1988.
5. Birkmayer G.D.: "Enzyme-based Assay fir Determining Effects of Exogenous and Endogenous Factors of Cellular Energy Production". Patentschrift, U.S. Patentnr. 6,248,552.
6. Wong R., Lopaschuk G., Zhu G., Walker D., Catellier D., Burton D., Teo K., Collins-Nakai R., Montague T.: Skeletal Muscle Metabolism in the Chronic Fatigue Syndrome. In vivo Assessment by 31P Nuclear Magnetic Resonance Spectroscopy. Chest 1992; 102;1716-22.
7. D. Grathwohl, M. Klann, H.M. Müller, H. Schlachter, A. Berg: Einfluß einer NADH-Supplementation auf die muskuläre Energiebereitstellung bei Menschen. Deutsche Zeitschrift für Sportmedizin, 52, 1/2001.
8. H. Schlachter, K. Nadlinger, M. Müller, G. Grathwohl, Dr. Storga Tomic, J. Birkmayer and A. Berg: Experience with a new in-vitro test to evaluate cellular NADH availability in athletes, 8th Int. Congress on Physical Education & Sport, 19-21 May 2000, Komotini, Greece.
9. Forsyth L.M., Preuss H.G., MacDowell A.L., Chiazze L. Jr., Birkmayer G.D., Bellanti J.A.: Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. Ann Allergy Asthma Immunol 1999; 82(2):185-191.
10. Rex A., Hentschke M.P., Fink H.: Examination of the Bioavailability of Reduced Nicotinamide Adenine Dinucleotide (NADH) in the CNS of the Anaesthetized Rat by Laser-Induced Fluorescence Spectroscopy. Biological Chemistry, 2001, in print.
11. Xu M., Zhang Jiren: The Reduced Coenzyme Nicotinamide Adenine Dinucleotide (NADH) Prevents Hepatic Cells from Apoptosis by Mitochondria. Int. J. Modern Cancer Therapy 2000, 3, 38-41.
12. Pelzmann et al.: manuscript in preparation