127 EFFECT OF FRUCTOSE INFUSION IN HEREDITARY XANTHINURIA: EVIDENCE FOR GTP DEGRADATION

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The rapid infusion of fructose is known to increase uric acid synthesis through consumption of ATP in fructose phosphorylation and conversion of AMP to IMP, cleavage of IMP, phosphorolysis of inosine, and oxidation of hypoxanthine and xanthine to uric acid. The congenital absence of xanthine oxidase provides an in vivo model further to elucidate the contribution of alternative pathways to fructose-induced hyperuricemia. Two brothers with hereditary xanthinuria were given a fructose infusion and the following was observed: (a) no change in the low levels of serum urate (0.4 and 0.6 mg/dl) and urinary uric acid (0.02 and 0.03 mmol/g creatinine) as compared to a control group who showed mean increases of 150 and 275 percent from the baseline values, respectively; (b) an increase in elevated baseline urinary xanthine from 1.7 and 1.3 to 2.7 and 1.8 mmol/g creatinine; (c) an elevation of plasma guanosine from undetectable values to 0.7 and 0.9 uM; and (d) an increase in the elevated plasma xanthine levels from 12.4 and 6.8 uM to 18.0 and 16.1 uM, as compared to a mean baseline value of 0.8 and increase to 3.6 uM in controls. These data suggest that GTP degradation contributes to fructose-induced hyperuricemia.

128 DIMINISHED TUBULAR SECRETION OF URATE IN GOUT NOT DEPENDENT ON SERUM URATE LEVELS

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To determine whether an impaired tubular transport mechanism for urate could differentiate the pathogenesis of gouty hyperuricemia and if serum urate influences the renal handling of uric acid, we conducted metabolic studies in 56 patients with primary gout. Tubular reabsorption of urate was normal. Tubular secretory rate was 29.3 $\pm$ 8.7 percent of filtered urate as compared to 42.4 $\pm$ 4.3 percent in 10 normal subjects for a similar urate filtered load ($P < 0.01$). Among 30 patients examined in the basal state and at pharmacologically reduced serum urate levels, 24 showed a diminished and 6 normal tubular urate secretion in both states of uricemia. According to the probenecid test, 45 patients evidenced a diminished uricosuric response and 11 normal urate excretion rates. This classification was similar to that obtained by the 24-h urinary urate excretion and was identical to that established by means of [2-^{14}C]uric acid in 8 selected patients. We conclude that an impaired tubular secretion of urate may differentiate gouty underexcretors from uric acid overproducers. Increased serum urate is not the cause but a consequence of the impaired tubular urate secretory mechanism in gout.

129 ROLE OF dATP IN THE INHIBITION OF NUCLEIC ACID SYNTHESIS IN ISOLATED NUCLEI.

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Nucleic acid synthesis was measured in nuclei isolated from proliferating lymphoblast cell lines that had been incubated with deoxyadenosine (dAdo) plus deoxycoformycin (dCf). Both RNA and DNA synthesis were inhibited in nuclei that were isolated from a T-cell line, CEM, following treatment with dAdo and dCf. Conversely, there was no inhibition of either RNA or DNA synthesis in the nuclei isolated from a B-cell line, WI-L2, or a dAdo kinase-deficient mutant of the T-cell line which had been incubated with dAdo plus dCf. Nucleotide measurements in the three cell lines implied that the accumulation of dATP in the intact cell was necessary for the inhibition of nucleic acid synthesis in the isolated nuclei. Saturating concentrations of all the nucleoside triphosphate precursors were present in the assays of the isolated nuclei. Thus, the inhibition of nucleic acid synthesis could not be explained by a depletion of nucleotide precursors following an inhibition of ribonucleotide reductase by dATP. After the isolation and washing procedure, no endogenous nucleotides could be detected in the isolated nuclei. The accumulation of dATP in the intact cell apparently damaged the ability of isolated nuclei to synthesize nucleic acids and this damage persisted even in the absence of dATP.

130 URATE BINDING α_2-GLOBULIN : SPECIFIC ANTIBODY PREPARATION.

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We reported (1) the isolation of an urate binding α_2-globulin from human serum. Now we wish to determine the physiologic role of this urate binding α_2-globulin in healthy subjects and gouty patients. Antibodies against purified α_2-globulin were prepared by rabbit immunization. Several injections of Freund's incomplete adjuvant mixed with an aqueous solution of α_2-globulin were repeated to increase immune response. Rabbit was bled by cardiac puncture. γ-globulin fraction was separated from the serum by ammonium sulphate precipitation. Double immunodiffusion in agar was used for semiquantitative analysis of the rabbit serum immunoglobulines. The formation of a single precipitation line between the purified α_2-globulin and its corrisponding antiserum can be utilized as a rough qualitative estimation of antibody purity. High purified antibodies were obtained from rabbit antiserum by affinity chromatography technique (α_2-globulin-Sepharose). These purified antibodies will be utilized to assay serum levels of α_2-globulin in healthy subjects and gouty patients.

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131 2'5'OLIGOADENYLATE SYNTHETASE IN HERPES VIRUS INFECTION AND AFTER INTERFERON TREATMENT

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Interferon plays an important role in the response of the entire organism to a viral infection. The level of interferon in serum is at present difficult to measure especially at low levels and transiently high levels so that interferon activity in virus infections has sometimes not been detected. Interferon measurements has thus been quite useless as a diagnosticum.

In vitro the 2'5'oligoadenylate synthetase has been shown to increase dramatically in a large variety of cells in culture after interferon treatment. This focus attention upon the possibility of using 2'5'oligoadenylate synthetase as a marker of interferon presence and by this as a dianosticum of virus infection. In the present study 2'5'oligoadenylate synthetase has been measured in mononuclear cells from Herpes zoster patients (N 7) and after interferon treatment of broncogenic carcinoma patients (N 7). It is shown that 2'5'oligoadenylate synthetase activities were increased in Herpes zoster patients (range 5-10 units/10^6 cells (1 unit converts 1 nmol/min)) and in broncogenic carcinoma patients after interferon treatment (range 2.7-8.4 units/10^6 cells) in comparison with normals (N 20) (range 2.5-0.4 units/10^6 cells). This confirms interferon induces 2'5'oligoadenylate activity in human virus infections.

132 IMMUNOPURINOGENIC ENZYMATIC ACTIVITY IN THE ACQUIRED IMMUNODEFICIENCY SYNDROME.

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Deficiencies of the purine catabolic enzymes adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) have been described in association with severe combined immunodeficiency disease and selective T-cell immunodeficiency disease respectively. Recently a selective T-cell acquired immunodeficiency syndrome has been described in homosexuals, drug addicts, Haitians and hemophiliacs. In an attempt to explore further metabolic mechanisms to account for this disorder we have quantitated erythrocyte and lymphocyte ADA and PNP activities using highly sensitive radiochemical methods in controls and seven patients with AIDS. Our results are as follows: 1) Erythrocyte ADA activity in controls and AIDS patients was 0.66 n mol/min/mg protein and 0.80 n mol/min/mg protein respectively. 2) Lymphocyte ADA activity was 6.86 n mol/min/mg protein for controls and 5.57 n mol/min/mg protein in AIDS. 3)Erythrocyte PNP activity was 2680 n mol/hr/mg protein for controls and 1618 n mol/hr/mg protein in the patients ($p<.0005$) 4)Lymphocyte PNP activity was 5892 n mol/hr/mg protein and 2740 n mol/hr/mg protein for controls and AIDS patients respectively ($P<.0025$). We conclude that: (1) Abnormalities in purine catabolic enzymes should be included in the disease spectrum of AIDS. (2) The causal relationship of decreased PNP activity in perpetuating the abnormal T-cell function in these patients remains to be determined (3) Alternatively the decreased PNP activity in AIDS may be secondary to the profound selective T-cell lymphopenia in this syndrome.