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Amino Acid Metabolism of Man
in
Health and Disease

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During the past year, satisfying progress has been made in our studies on the fundamental aspects of amino acid and protein metabolism as related to pediatrics, geriatrics and convalescent states. The accumulated experiences and their projections will be described briefly in this report.

1. Protein-Sparing Action of Carbohydrates.

Nitrogen balance and metabolic studies previously reported from this and other laboratories indicate that fructose of fructose-containing sugars are better protein spacers than dextrose. In order to secure experimental evidence regarding the biochemical dynamics of these observations, the effect of orally administered test doses of dextrose and fructose (1gm/K), on the metabolic nitrogen pool was determined in terms of the changes induced in one hour of the blood amino nitrogen levels of 40 fasting subjects (13 to 81 years). Total sugar and fructose blood levels were also measured. The results so obtained disclose that whereas the more readily utilized fructose makes an appreciable positive contribution to the metabolic nitrogen pool within one hour of administration, the less readily utilized dextrose does not. Thus, the greater protein sparing activity of fructose observed in nitrogen balance studies would seem to arise from the salvaging effects of rapidly formed fructose metabolites on the circulating nitrogen pool; perhaps via the transamination cycle.

Attempts to evaluate the orally administered protein equivalent of the blood protein spared by fructose in terms of blood amino nitrogen levels revealed that changes comparable to those observed with fructose were obtained by feeding 0.3gm/kilo of milk proteins.

The need for extending these studies to other carbohydrates i.e. starches, dextrose, lactose, etc., which commonly occur in human diets is obvious. Experimental evidence from animal studies indicate that marked metabolic and nutritional differences are to be expected. However, it would seem unwise to make an inference regarding the human on basis of the data secured from the studies on lower animals.

2. Studies in Parenteral Nutrition.

The data obtained in these studies with the invaluable collaboration of Doctors W. H. Arnold and D. R. Hays of the Department of Medicine, indicate that fructose or fructose-containing solutions I.V. are superior to dextrose solutions in terms of nitrogen sparing effect. Observations were made with 5% fructose, 10% fructose, 5% dextrose 10% dextrose and 10% invert sugar. When 3 liter infusions containing 150gm. of fructose, either as 5% fructose alone or as 10% solutions of invert sugar were used, comparable high nitrogen sparing action was observed. This showed a five fold increase when compared with 5% dextrose and a twelve fold increase when compared with 10% dextrose. When one or two liters of 5% fructose or 10% invert sugar

(each containing 50-100gm. of fructose) were used, the fructose exerted a somewhat greater nitrogen sparing effect than did the 10% invert sugar. When 150gm. of fructose were administered in the form of a 10% solution (given as 500 cc t.i.d.), the nitrogen sparing effect was greatly reduced.

A careful consideration of these findings leads to the opinion that 10% invert sugar or 5% fructose solutions are the nutrients of choice in this category of parenteral substances. Since a greater caloric input is achieved with the 10% invert sugar solutions, it would appear that this product should prove more generally useful than the 5% solution of fructose. The wisdom of this choice is further supported by practical consideration of relative cost and availability of invert sugar as compared to fructose.

In addition to the studies reported here, investigations on the biological value of dextrose and invert sugar in combination with a protein digest and ethanol given intravenously as the sole source of food were also done. It is clear from the data obtained in these studies that greater utilization of the infused nitrogen is achieved when the patient receives an adequate caloric supplement. The highest nitrogen balances were secured with the preparations containing alcohol. This result is believed to be due not only to the higher caloric input, but also in part to the sedation produced by this ingredient.

The results obtained with a product containing a protein hydrolysate of known high biological value in man in combination with dextrose or invert sugar which were also tested in this series showed

uniformly little or no improvement in the negative nitrogen balances of the patients. Chemical analyses of these products suggested that these poor results might be due to a destruction of tryptophane arising from an interaction with either the dextrose or invert sugar. Test tube experiments showed that chemically measurable tryptophane was reduced most rapidly in solutions containing 5% fructose or 10% invert sugar and more slowly in those containing 5% dextrose.

It appears from these experiences that the nutritional benefits available from the intravenous use of solutions of invert sugar, or fructose or amino acid digest are lost in part or in toto when these substances are combined in one multi-purpose preparation. In our experience, the degradation of nutritive properties of such solutions increases with standing. The change can be followed visually since the solutions change from a clear straw to a deep turbid brown color. The latter state is usually attained in six months at which time the solutions have been found to be biologically useless. These degraded preparations, however, did not produce any untoward symptoms. From the data available in this laboratory, it would appear that when the intravenous administration of both carbohydrates and protein hydrolysates is indicated, that they be given from separate containers, joined by a "Y" tube.

3. Studies in Rheumatic Heart Disease.

a. Effect of ACTH, Cortisone and Salicylates on Protein Synthesis in Man.

Studies were done on 38 children and 8 young adults who were in their second and third attacks of rheumatic fever. Analyses of the clinical response showed no statistically significant differences in the 3 forms of treatment upon the ultimate subsidence of the attacks. Biochemical measurements, however, showed much greater negative nitrogen balances in those treated with ACTH or Cortisone than in those receiving Salicylates. The high output of chromatographically determined urinary amino acids occurring with ACTH or Cortisone administration suggests that the nitrogen balance effects of those substances arise from a reduced rate of protein synthesis. Marked changes in blood amino acid patterns were also induced by ACTH and Cortisone but not by Salicylates given alone or in conjunction with p-aminobenzoic acid. These changes involved predominantly, increases in blood arginine, glutamic acid, serine, glycine, threonine, alanine, tyrosine and histidine. In addition, the appearance in the blood of unidentified peptides having Rf values 0.45-0.50 and 0.61-0.65 were noted with the administration of ACTH; especially the long-acting gel form. These peptides disappeared with termination of therapy providing additional evidence of the protein synthesis decelerating action of ACTH substances. Obviously, a therapeutic evaluation of these agents should consider their depletion effects on the metabolic nitrogen pool and stores.

b. Evaluation of Tests for Rheumatic Fever Activity.

In an excellent article summarizing the progress and perspectives in Rheumatic fever research, Dr. T. Luckett Jones has enumerated six questions for which we most need answers. The most basic of these questions appears to be the following: "How can we develop accurate diagnostic tests that would be as specific for rheumatic disease as the tests we now have for diphtheria, syphilis, etc.?" Our efforts along this line of inquiry have concerned themselves with a determination of chemical changes in the blood associated with the ESR measurement. These two year long investigations are now showing that diphenylamine reaction parallels closely the ESR measurements in children with acute rheumatic heart disease. In the chronic type of cases, the correlation of these two tests becomes erratic. In some instances, resumed activity of smoldering rheumatic heart disease cases can be forecast sooner by the diphenylamine reaction than the ESR measurement.

Recently, efforts have been made to establish the clinical and biochemical specificity of the diphenylamine reaction in diseases characterized by elevated ESR measurements. In nephrosis where consistently high ESR values prevail, we have found low diphenylamine reaction levels. In tubercular patients, however, good correlation exists between the two tests. Spectrophotometric studies of the diphenylamine reaction suggests that the derived color is due in part to desoxyribonucleic acid. This is an enzyme component of reactions concerned with protein synthesis in the mammalian organism.

4. Geriatric Nutrition.

Studies on the metabolism and nutrient requirements of the aged patients of St. Luke's Hospital and residents of the Osborn Memorial Home are being continued. The extended nitrogen balance measurements over a 4 year period on the study groups at the Osborn Home have shown that a remarkable constancy in food intake prevails in the aged; also, that their self-limited intake has had no significant effect on the usual criteria of nutritional status. These include hemoglobin, total plasma protein levels and body weight changes.

Cholesterol measurements on a limited group of these ladies has shown that no correlation prevails between body weight and cholesterol content of the blood. This is particularly significant since the average dietary fat intake of the home population is relatively high; 41% of the total calories are taken as fat. Electrophoretic measurements on some of these ladies during periods of infection, as indicated by elevated leucocyte counts, show a marked fall or absence of globulins. Investigations of the effect of dietary measures on the restoration of this blood fraction will be undertaken in the near future.

5. Pediatric Nutrition.

During the past year, 17 infants were studied with the collaboration of Doctors R. A. Higgons and G. M. Hyde, with regard to the effect of lysine supplementation of their diet which consisted primarily of a standard milk formula and additions of strained baby food.

consistent with current pediatric practices. The biological effects of the lysine were determined in terms of body weight and anthropometric changes; hemoglobin, total plasma proteins and blood lysine levels.

The results of these measurements indicate that a beneficial effect to most infants is attained from the lysine supplement in terms of all the criteria employed. This effect was noted in these infants, not only with respect to their own control periods, but also in comparison with control subjects who received no lysine supplement at all.

Our experiences with lysine supplemented bread in the toddler age group (12 children, 2.2-5.5 years) disclosed as others have found before us, that in general American children do not eat enough bread to make a measurable nutritional difference if a good animal protein diet such as is available in our hospital is provided. In the face of these mounting negative results, we gave five of these children a lysine supplement in their milk. In two of these five children, a significant positive growth response was noted.

6. Methodology.

During the past year, a simple and inexpensive apparatus for paper electrophoresis was designed and constructed. By means of this device, quantitative serum and plasma protein fractionations can be done on samples 0.025 to 0.059 cc of blood. This procedure also can be applied to a study of lipoprotein changes which occur in various

diseases and with advancing years. To further facilitate our investigations in geriatric nutrition and nephrosis, a micro method for the determination of cholesterol in finger prick quantities (0.050cc) of blood has been elaborated.

7. Organizational Activities.

In August, the responsible investigator attended the Food and Nutrition Gordon Research Conferences where he served as Chairman of the Symposium on the Biological Utilization of Isomers. He also presented a paper on the "Utilization of D-amino Acids by Man." Subsequently he was elected Vice-Chairman of the 1954 Food and Nutrition Conferences and Chairman-Elect of the 1955 meetings. In September he attended the International Congress of Physiology held in Montreal. During the past year he has served as contributor and referee for the forthcoming Handbook of Biological Data of the National Research Council. He continues as editorial referee for the Archives of Biochemistry and Physica, Journal of Laboratory and Clinical Medicine, the Journal of Clinical Nutrition, Analytical Chemistry and Agricultural and Food Chemistry.

A list of publications and presentations is appended.

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