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FEATURES PECULIAR TO NICOTINIC ACID METABOLISM IN ACUTE RESPIRATORY DISEASES

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Nicotinic acid - niacin - in the pyridine nucleotides (NAD, NADF, and their reduced forms) form a part of the prosthetic groups of dehrdrogenase, i.e. of key enzymes of intermediate matter exchange. In the liver of man are enzyme systems which convert tryptophan into nicotinic acid (Ye V Goryachenkova; Dalgliesh). However, this satisfies only a small part of the niacin requirements of the organism. The basic quantity of the vitamin must enter from without in the food. The health requirements of man include 20mg a day (I M Raskin). Nicotinic acid is quickly absorbed from the gastro-intestinal tract, amidated, and converted in tissue in coenzyme form.

The metabolism of nicotinic acid and pyridine nucleotides are in intimate connection with the function of the liver. Excess niacin in the NAD form can be accumulated in the liver in significant quantities and remain there a relatively short time (R M Azarkh). Only in liver cells is nicotinamide treated with methylation and converted into a basic metabolite - N_1-methylnicotinamide (MNA), leaving the organism in the urine. MNA is oxidized with the help of flavin enzymes into the so-called pyridons of the substance, mainly 6-pyridon (Knox and Grossman). A small quantity of 4-pyridon is always present in human urine; excretion of 2-pyridon sharply increases after ingesting niacin or triptophan (Chang and Johnson). The urine content of still another metabolite - nicotinamid-N_1-oxide - increases during destruction of liver NAD (Chaukin and Block; Bonavita et al).

During severe respiratory diseases and pneumonia which significantly disturb exterior breathing and impregnation of blood with oxygen (N S Molchanov, D I Pen), the effect, naturally, must show up in tissue breatning, in which nicotinamide enzymes play a direct role. Therefore, the study of the metabolism of nicotinic acid during severe sicknesses of the respiratory apparatus holds positive interest. Literature on this question is practically non-existant.

We observed 27 sick people, subsequently vaccinated by weakened A_2/21 influenza virus prepared at the Leningrad Institute of Vaccines and Serums, 21 sick with sporadic severe respiratory diseases, 12 sick with tonsillitis, and 8 with acute pneumonia. The age of the ill and healthy was from 17 to 35. Males predominated (43). All were observed under hospital conditions and received diet No. 15 without supplementary nicotinic acid. The daily ration contained an average of 17.5mg of niacin.

In the group vaccinated against influenza 13 men received internally hydrochloric amantadin (100mg twice a day for 9 days), and 14 were given placebo; 10 sick with acute respiratory diseases were given intranasal amantadin (50mg

3 times a day) for 3 days together with lactose and menthol, and 11 patients were given placebo (lactose with menthol). Those with tonsillitis were treated with injections of penicillir (5 days), and those with pneumonia received penicillin with streptomicin (average therapeutic dose was 7-10 days). The clinical picture was typical: acute respiratory diseases were not severe, and tonsillitis and pneumonia were of average severity. Antibiotic therapeutics in the last two groups brought toxicosis to a quick end and lowered the temperature, but local appearance of tonsillitis and pneumonia disappeared significantly later.

We judged the metabolism of nicotinic acid according to the contents of pyridine nucleotides (NAD and NADF) in whole blood and erythrocytes (by the method of Levitas, et al), as well as according to spontaneous removal in the daily urine of N_1-methylnicotinamid (fluorimetric method of Huff and Perlzweig with the modification of P D Starshova, 1962) and its 9-pyridon (spectrophotometric method of Knox and Grossman in the report of A M Petrunkina). The EF-3 electrofluorometer and SF-4A spectrophotometer were used. All these investigations were carried out in the acute phase of disease after 5-7 days and for those sick with pne monia 10-12 days after the second investigation.

Among the healthy (until vaccination against influenza) the level of pyridine nucleotides was 36.9±1.84mkg in 1ml of whole blood and 85.6±4.6mkg in 1ml of erythrocytes. These figures match the normal indicators obtained by many authors (Ya B Maksimovich and V V Osinskiy; Bertolini, et al). After 24 hours healthy people of the control group excreted 11±0.82mg of N_1-methylnicotinamid and 9.5±1.04mg of 6-pyridon of N_1-methylnicotinamid (6-P) in their urine. These facts also agree with the literature (E A Beyul, et al; A M Petrunkina; Huff and Perizweig). It was ascertained that penicillin and streptomycin were mixed with the urine in quantities larger than normaily found, but that this did not hinder the identification in it of N_1-methylnicotinamid (P D Starshov). No variations in the indicators studied by us were revealed in groups receiving or not receiving amantadin.

Two to three days after inhalation and intranasal administration of weakened A2 influenza virus to healthy individuals, 19 of the 27 people developed weak reactions (rhinitis, pharyngitis, subferile condition) lasting 1-3 days. On the third day after vaccination pyridine nucleotides in whole blood were at a 92.1± 6.4mg/ml level. Urine contained 12.9±1.4mg of N_1-methylnicotinamide and 8.7±1.4mg of 6-pyridon at this time. Thus, in this group during minimal expression of vaccine reaction no variation in nicotinic acid exchange could be ascertained.

Among those with sporadic severe respiratory diseases, at the height of the disease the level of pyridine nucleotides in whole blood had a tendency to decrease (33.6±2.16mkg/ml), and in erythrocytes it was significantly lower (67.7±4.6mkg/ml, $P<0.01$), than for the healthy. Excretion of N_1-methylnicotinamide and its 6-pyridone during this time, on the contrary, significantly exceeded the normal (19.6±2.7 and 15.1±1.3mg respectively, $P<0.01$). During convalescence (5-7 days after the first investigation) a distinct tendency to increase the level of pyridine nucleotides appeared in the blood and erythrocites (36.4±13 and 74±2.8mkg/ml respectively), but spontaneous removal of N_1-methylnicotinamid and 6-pyridon decreased to normal (12.9±1.3 and 11.7±0.85ml).

During the acute phase of tonsillitis the level of pyridine nucleotides in whole blood and erythrocytes remained practically undistinguished from the normal

(35.4±2.8 and 72±5.7mkg/ml), but the excretion of N_1-methylnicotinamide (14±3.8ml) and especially of 6-pyridon (21.4±5.3ml, $P<0.05$) exceeded the normal. Before discharge of the sick, regardless of the normal temperature and absense of clinical symptoms of disease, excretion of the last two indicators remained high (16.7±2.4 and 17.2±3.1ml respectively).

Among those with acute pneumonia the level of pyridine nucleotides in whole blood and erythrocytes during the climax of the disease was significantly lower than among the healthy (28.3±3.1 and 59.6±5mkg/ml respectively, $P<0.02$), but removal of N_1-methylnicotinamid and 6-pyridon was far higher than normal (29.8±9 and 21.7±4.8ml respectively, $P<0.05$). Six to eight days after treatment with antibiotics during normal temperature and satisfactory general condition, a tendency for the level of pyridine nucleotides in the blood and erythrocytes to increase (32.6±3.2ml and 70.3±6mkg/ml) appeared, but spontaneous secretion of N_1-methylnicotinamid and 6-pyridon continued at a high rate (respectively 20.7±4.1 and 20.7±5.5ml). At the end of 2-3 weeks with normal temperatures when neither physical nor X-ray indications of pneumonia any longer appeared, the pyridine nucleotide level in the blood and erythrocytes became normal (38.7±3.6 and 82±4mkg/ml). Excretion of N_1-methylnicotinamid and 6-pyridon at this time was significantly lower in comparison with the acute phase, but still was higher than among the healthy (18.5±3.0 and 15.6±1.8ml respectively).

Thus, those sick with acute inflamation and changes in various areas of the respiratory apparatus showed rather stereotypic deviation in metabolism of nicotinic acid. These consisted of lowered level of pyridine nucleotides in whole blood and particularly in erythrocytes, as well as in raised spontaneous removal of N_1-methylnicotinamid and its 6-pyridon. The expression and duration of the metabolic shift was in direct dependence on the intensity and duration of the inflamatory process. They were practically nonexistent during weakened vaccine reactions to injection of live weakened A_2 influenza virus. Minor and rapidly alleviated changes were observed during sporadic acute respiratory illness. More expressive and long-lasting pathological deviations in the metabolism of niacin were diagnosed during tonsillitis and, particularly, pneumonia.

Introduction of niacin into human metabolism significantly supplements diagnosis of the excretion of 6-pyridon in accordance with studied pyridine nucleotides in blood and N_1-methylnicotinamid in the urine. According to our data, in agreement with those of A M Petrunkina, from 6-pyridon comes 17-89% (with the average from 42 to 50% in various groups) of all methulated products of the urine.

The variation in the metabolism of niacin in evidence during acute diseases of the respiratory apparatus recalls analogous shifts during many severe infectious diseases (V R Bobyleva; M A Borisova; A A Novakovskaya; K V Bunin; N S Krasnova; P D Starshov) and other pathological conditions accompanying breakdown or insufficient formation of protein (L A Cherkes et al; N M Filchagin; A N Tikhomirova, et al).

The mechanism of changing nicotinic acid metabolism during acute inflamatory diseases of the respiratory organs can be connected both with increased breakdown of tissue protein and with decreased formation of protein from food due to lowered appetite during the acute phase of the disease, as well as with intensified metabolism of this same niacin and niacin-containing enzymes in connection with inflamation and

disturbance of tissue breathing. The latter has, obviously, compensator-adaptative significance. The sick organism in the acute phase loses a significant quantity of niacin, which can lead to comparative niacin deficiency. With the goal of compensating for this loss, supplementary vitamin was administered. It was efficiently ingested in food in a daily dose of 40-80mg granulated. Such a vitamin dosage does not lead to excessive stress of the metabolic processes and fulfills the requirements of nicotinic acid during all stages of the disease.

Conclusions

1. During sporadic acute respiratory sicknesses, tonsillitis, and pneumonia, stereotypic deviations in the metabolism of nicotinic acid, including decreased level of pyridine nucleotides in whole blood and erythrocytes and in raised spontaneous removal in the urine of N_1-methylnicotinamid and its 6-pyridon were observed.

2. Expressivity and duration of metabolic shifts of nicotinic acid is found in direct relation to the intensity and duration of inflamatory changes of the breathing apparatus.

3. To compensate for the losses of nicotinic acid in the acute phase of the disease, addition of the vitamin in the food in a daily dose of 40>80mg, granulated, was ordered.

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