The Effect of Pyrroline-5-carboxylic Acid on Nucleotide Metabolism in Erythrocytes from Normal and Glucose-6-phosphate Dehydrogenase-deficient Subjects*

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Pyrroline-5-carboxylate, the intermediate in the interconversion of proline, ornithine, and glutamate, increases 5-phosphoribosyl 1-pyrophosphate (PP-ribose-P) and purine nucleotide formation in intact human erythrocytes. We proposed that: 1) pyrroline-5-carboxylate is converted to proline by pyrroline-5-carboxylate reductase with concomitant oxidation of NADPH, 2) NADPH augments glucose-6-phosphate dehydrogenase activity, and 3) production of ribose-5-phosphate via the pentose shunt is increased. Since glucose-6-phosphate dehydrogenase plays a central role in this proposed mechanism, we examined the responsiveness of glucose-6-phosphate dehydrogenase-deficient erythrocytes to pyrroline-5-carboxylate. We compared erythrocytes from four Sardinian glucose-6-phosphate dehydrogenase-deficient subjects and four Sardinian normal controls. Without pyrroline-5-carboxylate treatment, the levels of pentose phosphate pathway activity, PP-ribose-P synthesis, and four Sardinian normal controls. These findings strongly support our proposed mechanism for the pyrroline-5-carboxylate effect on nucleotides. Furthermore, the markedly different capacities for nucleotide synthesis in the two populations with pyrroline-5-carboxylate treatment suggest a role for pyrroline-5-carboxylate-mediated modulation of nucleotide metabolism in normal cells.

The production of PP-ribose-P is an important point of regulation in the synthesis of purine, pyrimidine, and pyridine nucleotides (1, 2). A number of metabolic factors participate in the regulation of PP-ribose-P, including the critical activation of PP-ribose-P synthetase (ribose-phosphate pyrophosphokinase, EC 2.7.6.1) by inorganic phosphate (3, 4). The human erythrocyte with its less complex metabolism of nucleotides has proved to be a useful model for studying the regulation of PP-ribose-P (5). Using erythrocytes, we recently showed that pyrroline-5-carboxylic acid, an intermediate in the interconversion of proline, ornithine, and glutamic acid, initiates a chain of biochemical events resulting in increased PP-ribose-P and nucleotide formation (6-8). The mechanism for this effect is dependent on redox activation of the pentose phosphate pathway (9-12). Since glucose-6-phosphate dehydrogenase (EC 1.1.1.49) catalyzes the rate-limiting step in the pentose phosphate pathway, a deficiency of this enzyme should abrogate the stimulatory effect of pyrroline-5-carboxylate. To test our hypothesis, we performed a series of experiments in erythrocytes from patients with Mediterranean type glucose-6-phosphate dehydrogenase deficiency. We measured pentose phosphate pathway activity, PP-ribose-P synthesis, IMP formation from hypoxanthine, and incorporation of differentially labeled glucose into the ribose moiety of IMP. We found that erythrocytes deficient in glucose-6-phosphate dehydrogenase activity had markedly impaired responses to pyrroline-5-carboxylate in all these metabolic functions. These studies not only support the pyrroline-5-carboxylate-mediated metabolic cascade, but also provide a framework for comparing the relative contributions of the oxidative and nonoxidative arms of glucose metabolism to PP-ribose-P production.

MATERIALS AND METHODS

Cells—Venous blood was obtained by venipuncture from four subjects with Mediterranean type glucose-6-phosphate dehydrogenase deficiency and from four normal controls. These blood samples were kept in citrate/phosphate/dextrose solution at 4 °C and sent by air from Sardinia to New York. Upon receipt in New York, the blood samples were aliquoted, packaged at 4 °C, and shipped to Bethesda where the incubations for the metabolic studies were performed on the same day. Upon receipt, erythrocytes were washed three times with 10 volumes of normal saline, and the leukocytes were removed by established procedures (15). Extracts were prepared from aliquots of these red cells for measurement of pyrroline-5-carboxylate reductase activity and glucose-6-phosphate dehydrogenase activity.

Pentose Phosphate Activity—Pentose phosphate activity was assessed using the oxidation of 1-14C-labeled glucose by a method previously described (9). In brief, 50 μL of red cells were incubated in an Erlenmeyer flask with 1 ml of Earle’s balanced salt solution. The concentration of glucose was 2.5 mM, and 2 μCi of [1-14C]glucose/assay were used. The flasks were gassed with 98% oxygen and 2% CO2 and sealed with a serum stopper containing a plastic center well.
Following a 1-h incubation, 0.3 ml of Hypoxanthine was placed within the center well, and 0.3 ml of 6 N sulfuric acid was injected into the incubation mixture to stop the reaction. Evolved \(^{14}\)CO\(_2\) was trapped in Hypoxanthine with an equilibration period of 45 min at room temperature. The radioactivity contained in Hypoxanthine was measured by liquid scintillation spectrometry.

**Incubation of Erythrocytes for PP-Ribose-P Production and Incorporation of Hypoxanthine into ZMP-Erythrocytes**

For measurement of IMP formation, hypoxanthine (25 \(\mu\)M) was added. In certain preparations, glucose was differentially labeled with \(^{14}\)C in either C-1 or C-6. Incubation continued for an additional 60 min. In those incubations in which PP-ribose-P was measured, the cell suspension was boiled for 45 s in a boiling water bath after incubation. Samples were then quickly chilled and centrifuged at 10,000 \(\times\) g, and the supernatant was stored at -20 °C for assays of PP-ribose-P concentration on the following day. For those preparations in which the production of nucleotides was measured, we recovered the incubated cells by microfuge centrifugation at 10,000 \(\times\) g for 1 min, and the cell pellet was taken up in 12% trichloroacetic acid.

After precipitated proteins were removed by centrifugation, supernatants were saved for nucleotide separation by high pressure liquid chromatography.

**Enzyme Assays**

The activity of pyrroline-5-carboxylate reductase was assessed by a previously described method (15) using a specific and sensitive radioisotopic assay. The activity of glucose-6-phosphate dehydrogenase was measured by a previously described method (16).

**PP-Ribose-P Concentration**

The concentration of PP-ribose-P in the red cell extract was measured with a radioisotopic enzyme assay that has been previously described (17). In brief, we incubated [carboxyl-\(^{14}\)C]orotic acid with orotate phosphoribosyltransferase and orotidine-monophosphate decarboxylase. The amount of \(^{14}\)CO\(_2\) generated by this incubation is quantitatively dependent on the amount of PP-ribose-P. The recovery of PP-ribose-P by our method of extraction and assay is 85%.

**High Pressure Liquid Chromatography**

The procedure for nucleotide separation was our adaptation (7) of a procedure described by Brown and Parkey (18). In brief, a Whatman Partical 10 SAX ion exchange column was used. The low concentration eluent was 0.007 M KH\(_2\)PO\(_4\) at 0.007 M KCl, pH 3.5, and the high concentration eluent was 0.25 M KH\(_2\)PO\(_4\) at 0.3 M KCl, pH 4.5. An aliquot (150 \(\mu\)l) of the extract was applied to the column and a model 660 solvent program was monitored. Incubation was at 37 °C with a convex gradient with a flow rate of 1 ml/min. The gradient time was 30 min from 100% low concentration eluent to 100% high concentration eluent. After completion of the gradient, the column was eluted for an additional 40 min with 100% high concentration gradient. The optical density of the effluent was monitored at 254 nm, and the amount in each peak was calculated by the data module (Waters Associates) with the use of external standards. To quantify the incorporation of either \(^{14}\)C]hypoxanthine or differentially labeled \(^{14}\)C]glucose into IMP, we collected the effluent in 0.5-ml fractions and determined the radioactivity in each fraction by liquid scintillation spectrometry.

**RESULTS**

**Enzyme Levels**

As shown in Table I, glucose-6-phosphate dehydrogenase deficiency in our population was confirmed by assay of enzyme activity. The activity of erythrocytes from normal controls was 8.64 ± 0.80 units/g of hemoglobin, and the level in the affected population was 0.45 ± 0.20. Thus, our glucose-6-phosphate dehydrogenase-deficient population had approximately 5% of normal red cell enzyme levels. The activity of erythrocyte pyrroline-5-carboxylate reductase was measured under \(V_{max}\) conditions. With NADH as cofactor, the activity in normals was 16.8 ± 4.0 units/g of hemoglobin and in glucose-6-phosphate dehydrogenase-deficient subjects was 20.1 ± 6.02. With NADPH as cofactor, the activity was 2.8 ± 0.46 and 3.3 ± 1.01 in normal and glucose-6-phosphate dehydrogenase-deficient subjects, respectively.

**Pentose Phosphate Pathway Activity**

As shown in Fig. 1, the level of pentose phosphate activity in glucose-6-phosphate dehydrogenase-deficient cells was similar to that in normal cells. However, in the presence of 0.5 mM pyrroline-5-carboxylate, the activity in normals increased more than 7-fold (\(p < 0.001\)), whereas the glucose-6-phosphate dehydrogenase-deficient cells showed no increase. Thus, in spite of the similarity in the levels of pentose phosphate activity in the resting state, the levels of activity in the presence of pyrroline-5-carboxylate was markedly different in the two populations.

**PP-Ribose-P Levels**

Since the activity of PP-ribose-P synthetase is activated by inorganic phosphate, we measured PP-ribose-P levels in cells incubated with 25 mM phosphate. As shown in Fig. 1, the levels were 159.0 ± 35.8 and 102.5 ± 14.9 nmol/ml of cells in normal and glucose-6-phosphate-deficient cells, respectively. This difference was not statistically significant. When pyrroline-5-carboxylate was added at a concentration of 0.5 mM to the incubation medium, marked differences between the two populations emerged. In glucose-6-phosphate dehydrogenase-deficient cells, pyrroline-5-carboxylate produced no increase in PP-ribose-P levels. By contrast, with pyrroline-5-carboxylate, a 3-fold increase in normal cells was observed. Under these conditions, the levels in normal cells became markedly higher than those in glucose-6-phosphate dehydrogenase-deficient cells.

**The Formation of IMP from Hypoxanthine**

We assessed the capacity of the incubated erythrocytes to form IMP from hypoxanthine in the presence of 25 mM inorganic phosphate. We calculated net IMP formation by subtracting the levels before the addition of hypoxanthine from the levels after the incubation with hypoxanthine. As shown in Fig. 1, IMP formation rates were slightly higher in normal as compared to glucose-6-phosphate dehydrogenase-deficient cells, but this difference was not statistically significant. However, the addition of pyrroline-5-carboxylate increased formation rates in normal cells, but was without effect in glucose-6-phosphate dehydrogenase-deficient cells. Thus, in the presence of pyrroline-5-carboxylate, levels of IMP formation were markedly higher in normal cells than in glucose-6-phosphate dehydrogenase-deficient cells (\(p < 0.001\)).

**The Incorporation of Differentially Labeled Glucose into IMP**

We asked whether the oxidative or the nonoxidative branch of glucose metabolism supplied the ribose incorporated into nucleotides with pyrroline-5-carboxylate treatment. The quantitative incorporation of glucose labeled with \(^{14}\)C in either C-1 or C-6 was used to ascertain the source of the ribose incorporated into nucleotide. Interpretation of these results is based on the fact that glucose labeled at C-1 would be lost
FIG. 1. The effect of pyrroline-5-carboxylate in normal and Glu-6-P dehydrogenase-deficient erythrocytes. Erythrocytes were incubated as described under “Materials and Methods.” The duration of incubation was 60 min. Under the respective assay conditions, the measured pentose phosphate activity (A), PP-ribose-P formation (B), and IMP formation (C) were linear with time. The concentration of ~-pyrroline-5-carboxylate was 0.5 mM; each point represents duplicate determinations on normal (A) and Glu-6-P dehydrogenase-deficient (0) erythrocytes. The boxes enclose mean ± S.D. Based on the Student’s t test, the differences between normal and Glu-6-P dehydrogenase-deficient cells in control incubations were not significant (p > 0.1), nor were the differences between control and pyrroline-5-carboxylate-treated incubations in Glu-6-P dehydrogenase-deficient cells (p > 0.6). In contrast, the differences between control and pyrroline-5-carboxylate (PSC)-treated incubations in normal cells were highly significant (p < 0.01). RBC, red blood cells.

TABLE II

The incorporation of differentially labeled glucose into inosine monophosphate in normal and Glu-6-P dehydrogenase-deficient erythrocytes

The data represent mean ± S.D. of duplicate determinations on each of four subjects. Isolated erythrocytes were incubated as described under “Materials and Methods.” The concentration of hypoxanthine was 25 μM, and the concentration of pyrroline-5-carboxylate where indicated was 0.5 mM. The concentration of glucose was 2.5 mM and either [1-14C]glucose (10 μCi) or [6-14C]glucose (10 μCi) was added to parallel incubations. The duration of incubation was 60 min. Cells were spun down in a Microfuge centrifuge and the pellet take up in 1 ml of 12% trichloroacetic acid, vortexed, and recentrifuged. Nucleotides in the supernatant were analyzed by high pressure liquid chromatography. The amount of IMP pool was measured by obtaining the absorbance at 254 nm, and the incorporation of label into IMP was quantitated by measuring the radioactivity in 1-ml fractions of column effluent.

| No. of subjects | C-1-labeled | C-6-labeled | IMP pool |
|-----------------|-------------|-------------|----------|
|                 | dpm x 10^4/ml cells | nmol/ml cells | dpm x 10^4/ml cells | nmol/ml cells | nmol/ml cells |
| Normal control  | 4           | 0.26 ± 0.034 | 133 ± 23.5 | 0.17 ± 0.039 | 135 ± 19.7 | 206 ± 14.3 |
| Normal + pyrroline-5-carboxylate | 4 | 0.26 ± 0.041 | 88 ± 19.8 | 0.99 ± 0.303 | 509 ± 156.7* | 600 ± 142.8* |
| Glu-6-P dehydrogenase-deficient control | 4 | 0.25 ± 0.055 | 125 ± 28.8 | 0.21 ± 0.064 | 120 ± 41.9 | 174 ± 35.2 |
| Glu-6-P dehydrogenase-deficient + pyrroline-5-carboxylate | 4 | 0.21 ± 0.044 | 101 ± 19.2 | 0.20 ± 0.058 | 104 ± 30.5* | 180 ± 47.8* |

* Different from normal control as obtained by Student’s t test (p < 0.01).
* Different from normal + pyrroline-5-carboxylate (p < 0.01).

to CO₂ on being converted to ribose-5-phosphate by the oxidative arm. Thus, C-1-labeled glucose would contribute labeled ribose only via the nonoxidative arm, whereas C-6-labeled glucose would contribute via both the nonoxidative and the oxidative arms. As shown in Table II, under control conditions, essentially all of the ribose was derived from the nonoxidative arm of glucose metabolism. There was no difference between the incorporation of [6-14C]glucose and [1-14C]glucose into IMP. As expected, under control conditions, the incorporation of both [1-14C]glucose and [6-14C]glucose was not statistically different between normal and glucose-6-phosphate dehydrogenase-deficient cells. However, when cells
were stimulated with pyrroline-5-carboxylate, the incorporation of [6-14C]glucose was markedly increased in normal cells. In marked contrast, no increase was seen in glucose-6-phosphate dehydrogenase-deficient cells. Furthermore, in normal cells, the pyrroline-5-carboxylate-stimulated production of IMP appeared to use ribose derived exclusively from the oxidative arm. Based on the initial specific activities of radiolabeled glucose, the amount of pentose contributed by the oxidative arm was closely correlated with the net synthesis of IMP as measured by the increase in pool size. The ratio of ribose derived from the oxidative arm to total IMP formation was 1.08 ± 0.08. Thus, with pyrroline-5-carboxylate stimulation, the necessary pentose incorporated into IMP was totally derived from the oxidative arm. Although there was a modest decrease in the incorporation of C-1 glucose into IMP with pyrroline-5-carboxylate treatment, the decrease was not statistically significant.

**Discussion**

We hypothesized that pyrroline-5-carboxylate, the intermediate in the interconversions of proline, ornithine, and glutamate, provides a regulatory link between amino acid and nucleotide metabolism. The mechanism for this regulatory link is based on a redox-dependent cascade initiated by the conversion of pyrroline-5-carboxylate to proline (19). The enzyme mediating this conversion, pyrroline-5-carboxylate reductase, is the only enzyme of the proline-ornithine-glutamate metabolic system found in human erythrocytes. The activity of pyrroline-5-carboxylate reductase in red cells is comparable to that of major red cell enzymes. Furthermore, there are qualitative kinetic differences in red cell pyrroline-5-carboxylate reductase as compared to that from cultured cells. The red cell enzyme has high affinity (low $K_m$) for NADPH and is inhibited by NADP+, but not by proline (12). The oxidation of NADPH by pyrroline-5-carboxylate reductase increases the flux of carbons through the pentose phosphate pathway, increases the production of PP-ribose-P, and increases the incorporation of purine bases to their respective monophosphates (6, 7). Since the activity of glucose-6-phosphate dehydrogenase in situ is critically dependent on the ratio of NADP+ to NADPH (20), regulation of the level of glucose-6-phosphate dehydrogenase appears to be the likely mechanism for the pyrroline-5-carboxylate-initiated metabolic cascade.

The inability of pyrroline-5-carboxylate to stimulate pentose phosphate pathway, PP-ribose-P production, and incorporation of hypoxanthine into IMP in glucose-6-phosphate dehydrogenase-deficient erythrocytes provides strong support for the aforementioned hypothesis. Although direct effects of pyrroline-5-carboxylate on the activity of PP-ribose-P synthetase or hypoxanthine-guanine phosphoribosyltransferase have not been directly ruled out, these effects seem unlikely because of the differential response to pyrroline-5-carboxylate in normal and glucose-6-phosphate dehydrogenase-deficient cells.

The pyrroline-5-carboxylate effect on nucleotides depends on the redox activation of the pentose phosphate pathway. Interestingly, the relative importance of the oxidative (glucose-6-phosphate dehydrogenase-dependent) and nonoxidative arms of glucose metabolism as the source of ribose continues to be a topic of debate (2, 21). Relevant to this debate, a number of investigators have emphasized the importance of redox regulation at the level of glucose-6-phosphate dehydrogenase. Eggleston and Krebs (20) suggested that at physiologic redox ratios, flux through glucose-6-phosphate dehydrogenase is almost nonexistent. Thus, the true capacity of the oxidative arm is demonstrable only if the redox-dependent metabolic pathway has been opened. Under basal conditions, the nonoxidative arm is the predominant source of ribose. Nevertheless, under conditions of carbohydrate limitation, cultured cells derive their complement of nucleotide ribose almost entirely from the oxidative arm (22). Whether this shift is mediated by a redox-dependent mechanism is not known.

Based on studies in red cells and cultured fibroblasts deficient in glucose-6-phosphate dehydrogenase activity, some investigators consider the contribution made by the oxidative arm to be insignificant (4). These studies showed that under the reported experimental conditions, glucose-6-phosphate dehydrogenase-deficient cells were able to maintain PP-ribose-P pools similar to those in normal cells. This is not surprising since pentose phosphate pathway activity under resting conditions is similar in normal and glucose-6-phosphate dehydrogenase-deficient cells, a finding explainable by the markedly different NADP+/NADPH ratios between normal and glucose-6-phosphate dehydrogenase-deficient cells (23). Thus, glucose-6-phosphate dehydrogenase-deficient cells have a pentose phosphate pathway functioning at a much higher percentage of total capacity than that in normal cells. Surprisingly, in some studies, even when methylene blue was used to activate the pentose phosphate pathway, no significant differences appeared between normal and glucose-6-phosphate dehydrogenase-deficient cells in their PP-ribose-P levels (4). However, these studies did not include the net production of nucleotides as a measurement. Furthermore, the use of methylene blue, an antioxidant, as an activator of the pentose phosphate pathway may affect PP-ribose-P levels by altering overall energy metabolism. In cultured cells, exposure to methylene blue produces rapid dephosphorylation with a marked decrease in ATP and ADP levels and a concomitant increase in AMP levels (24). By contrast, pyrroline-5-carboxylate offers a number of advantages as a redox regulator. It is a naturally occurring intermediate, and its effects are enzyme-mediated. The activity of the mediating enzyme pyrroline-5-carboxylate reductase is itself sensitive to redox regulation (12). Thus, pyrroline-5-carboxylate can regulate the redox-dependent metabolic gate without detrimentally dephosphorylating nucleotides. Using pyrroline-5-carboxylate, we found striking differences between normal versus glucose-6-phosphate dehydrogenase-deficient erythrocytes in their capacities to produce PP-ribose-P and to incorporate hypoxanthine to IMP. These observed differences suggest that the pentose phosphate pathway, i.e., the oxidative arm, makes a critical contribution to the ribose phosphate pool.

The importance of inorganic phosphate in regulating PP-ribose-P levels has been supported by a variety of studies (2-4). The mechanism is related most likely to the activation of PP-ribose-P synthetase (2). Importantly, pyrroline-5-carboxylate increases both PP-ribose-P production and nucleotide formation over that of phosphate alone, even when phosphate is at optimal concentrations (7). Thus, phosphate is necessary but not sufficient to maximize the production of PP-ribose-P and nucleotides. Of course, the relative capacity to synthesize nucleotides in normal and glucose-6-phosphate dehydrogenase-deficient cells can be meaningfully compared only when PP-ribose-P synthetase is not the rate-limiting factor. In other words, assessment of the relative importance of the oxidative and nonoxidative arms in generating ribose moieties are interpretable only if phosphate concentrations are adequate to activate PP-ribose-P synthetase.

Although our studies show that glucose-6-phosphate dehydrogenase is necessary for the pyrroline-5-carboxylate activation of PP-ribose-P and nucleotide production, we are
uncertain as to the physiologic significance of this stimulation as well as the pathophysiologic significance of this newly defined defect in glucose-6-phosphate dehydrogenase-deficient cells. Although drug- and fava bean-induced hemolysis are associated with increased oxidative stress for the red cell (25), it is not clear whether the oxidative stress is primary or secondary to an effect on other tissues. Nevertheless, our studies suggest that glucose-6-phosphate dehydrogenase-deficient cells not only are deficient in their response to oxidative stress, but also have a defect in their capacity to produce PP-ribose-P and incorporate purine bases into nucleotides. Whether this mechanism contributes to the pathophysiology of the clinical syndrome in patients with glucose-6-phosphate dehydrogenase deficiency remains to be determined.

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