Deoxyribose-5-Phosphate Aldolase Deficiency—
a Harmless Inborn Error of Metabolism

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Evidence is presented that a deficiency of 2-deoxyribose-5-phosphate aldolase was present in a previously
described patient who excreted metabolites of 2-deoxyribose in his urine. Minor clinical abnormalities
present did not appear related to this disorder.

In previous reports (Truscott et al., 1979a,b) we
described the excretion of a number of metabolites of 2-
deoxyribose in a patient who was thought to have
cataracts and developmental delay. We now present
evidence that the abnormal metabolites in the urine of
this patient result from deficiency of the enzyme 2-
deoxyribose-5-phosphate aldolase (EC 4.1.2.4). Follow-
up assessment of the patient has revealed that he does
not have true cataracts and that his mildly delayed
development may be explained by his social circum-
stances. It is considered that deoxyribose-5-phosphate
aldolase deficiency may be a harmless inborn error of
metabolism.

CASE REPORT
The patient (J.S.) was the only child of unrelated Greek
parents and has been under the care of the Royal
Children's Hospital, Melbourne, since 3 months of age.
Strabismus, associated with marked astigmatism, and
bilateral ocular abnormalities, which were initially
thought to be cataracts, associated with mild de-
velopmental delay, poor feeding and recurrent vomiting
led to his investigation. Both parents had severe
psychiatric disturbances and many of his problems have
been due to emotional deprivation and abnormal
rearing.

Shit lamp investigation at 9 months revealed that the
suspected cataracts were really anterior lens capsular
opacities. Urinary amino acids, organic acids and sugars
were studied. Gas chromatography of the standard
ether/ethyl acetate extracts of urine revealed a
moderate amount of 2-deoxyerythropentono-1,4-
lactone; use of different extraction systems showed that
large amounts of a number of deoxyribose metabolites
were present in the urine (Truscott et al., 1979a,b).

Since the initial presentations, the seriously disturbed
family situation has persisted, making assessment of his
mental development very difficult. Until 3 years of age
brief periods at home with his schizoid mother
alternated with periods in hospital or babies' homes. He
has lived in an institution for the past 3 years and has
made better developmental progress. However, his
mother's regular visits cause emotional disturbance.
Motor skills are normal for his age of 6 years, but speech
and social skills are delayed. It is impossible to know
whether any true mental retardation is present, but this
is regarded as unlikely. Physical growth and health are
normal.

MATERIALS
Eagle's basal medium and fetal calf serum were obtained
from Flow Laboratories, polymyxin from Wellcome,
Australia Ltd. and neomycin from Hoechst-Roussel
Pharmaceuticals. Deoxyribose-5-phosphate was pur-
chased from Sigma Chemical Co. and semicarbazide
from B.D.H. Chemicals Ltd. Hoechst 33258 stain was
obtained from Hoechst. Other chemicals were of
analytical reagent grade.

METHODS
Fibroblast cultures were established from forearm skin
biopsies and grown in Eagle's basal medium with 10%
fetal calf serum and 1.5 μg/ml each of neomycin and
polymyxin. The cultures were screened regularly for
mycoplasma contamination using Hoechst 33258 stain
as described by Chen (1977). The cells were harvested
using trypsin/EDTA, washed in phosphate-buffered
saline and resuspended in 50 mmol/l potassium phos-
phate, pH 7.4. They were disrupted by sonication on ice
(Branson Sonic Power Co. Sonifier, 6 x 5 s pulses,
output setting 20% of maximum) and the sonicates
centrifuged at 10 000 g for 5 min. The supernatants were
used for assay.

Haemolysates were prepared from 5–10 ml blood
samples collected into heparinized tubes. The red cells
were collected by centrifugation, washed twice with
0.154 mol/l sodium chloride and lysed with an equal
volume of distilled water. Cell membranes were removed
by centrifugation at 10 000 g for 5 min.

Protein concentrations were measured by the method
of Lowry et al. (1951) and haemoglobin by the optical
density at 540 nm after conversion to cyanmethem-
globin.
Deoxyribose-5-phosphate aldolase assays

The formation of acetaldehyde from deoxyribose-5-phosphate was followed using a modification of the assay described by Burbridge et al. (1950). The reaction mixture contained 5 mmol/l deoxyribose-5-phosphate, 5 mmol/l sodium citrate, 40 mmol/l potassium phosphate, pH 7.3 and haemolysate or cell extract in a total volume of 0.5 ml. The reaction was carried out in a glass liquid scintillation vial in which was placed a small glass tube containing 0.2 ml 6.7 mmol/l semicarbazide in 0.2 mol/l potassium phosphate, pH 7.0. The vial was sealed with a gas tight rubber stopper. Acetaldehyde released during the incubation (60 min at 37°C) was trapped in the semicarbazide solution and its concentration determined from the absorbance at 224 nm after dilution to 1.0 ml with water. The amount of acetaldehyde formed during the reaction was determined from a standard curve over a range of 0–100 nmol. The standard curve was prepared from reaction mixtures without haemolysate to which were added various amounts of acetaldehyde. These were treated in the same manner as the assay samples to allow for recovery of acetaldehyde from the reaction mixture.

RESULTS

Blood samples from the patient, his mother and a group of ten normal young adult females were obtained. The father was unavailable for study. The results of 2-deoxyribose-5-phosphate aldolase assays of these samples are summarized in Table 1. No activity could be detected in any of a number of blood samples from the patient. Haemolysates from the mother had activity intermediate between that of the patient and controls.

A cultured fibroblast line was established from the patient and deoxyribose-5-phosphate aldolase activity in cell extracts compared to four control cell lines. These results are also presented in Table 1. It is not known if the very low level of activity measured in the patient’s cells is significantly different from zero in this assay.

DISCUSSION

The patient described in this report has a deficiency of 2-deoxyribose-5-phosphate aldolase as defined by undetectable activity in red blood cells and minimal activity in cultured fibroblasts. This defect was first suspected because of the urinary excretion of 2-deoxyerythropentonic acid, 2-deoxyerythropentono-1,5-lactone, 2-deoxyerythropentono-1,4-lactone and 2-deoxyribitol–metabolites of 2-deoxyribose.

The 2-deoxyribose-5-phosphate generated during catabolism of DNA is metabolized by deoxyribose-5-phosphate aldolase to acetaldehyde and glyceraldehyde-3-phosphate. The enzyme was first described by Racker (1952), in mammalian liver and thymus and in several bacterial species. The enzyme has been purified from rat liver by Roscoe and Nelson (1964) and Groth (1967) and from human erythrocytes by Jedrzniaik and Lionetti (1970). The enzyme is subject to activation by a number of polycarboxylic acids, particularly citrate (Jiang and Groth, 1962), and appears to have an essential sulphydryl group (Roscoe and Nelson, 1964; Groth, 1967). The physiological role of the enzyme is at present poorly understood, although it is generally thought that the reaction in vivo is in the direction of deoxyribose-5-phosphate catabolism. The activity of the enzyme is increased in malignant tissues compared to normals (Boxer and Shonk, 1958) and the activity varies during the cell cycle in rat hepatoma cells with a peak in activity during the G2 phase (Lincoln and Hoffee, 1979).

While this patient is the only one so far described with 2-deoxyribose-5-phosphate aldolase deficiency, it is possible that this defect may be relatively common. In screening 58 normal subjects by the erythrocyte assay described, four were found with levels of activity comparable to that of the patient’s mother, suggesting that the heterozygote frequency may be quite high. Persons homozygous for this mutation could escape detection because the compounds excreted by the patient are poorly extracted from urine by the systems generally used in screening by gas chromatography–mass spectrometry and because there seems to be no specific clinical disorder.

We suggest that deoxyribose-5-phosphate aldolase deficiency is a benign condition.

Mr G. Keith assessed the ocular lesion. Dr Chappel was in receipt of the Elizabeth Sweet Fellowship of the University of Melbourne; Dr Truscott held a grant from the National Health and Medical Research Council of Australia.

References


Table 1 2-deoxyribose-5-phosphate aldolase activity in patient, mother and controls in haemolysates and in cultured fibroblasts

<table>
<thead>
<tr>
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<th>Controls</th>
<th>Patient</th>
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<tbody>
<tr>
<td>Haemolysate</td>
<td>28.5 ± 3.1 (10)</td>
<td>not detectable</td>
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<tr>
<td>Fibroblast extracts</td>
<td>68.8 ± 3.5 (4)</td>
<td>1.4</td>
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</table>

*Activity expressed as nmol acetaldehyde formed/mg haemoglobin per h mean ± sd
‡Activity expressed as nmol acetaldehyde formed/mg protein per h mean ± sd
‡Numbers in brackets are number of subjects or cell lines

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