The role of the glutathione and its related enzymes in the susceptibility of the Egyptian Down syndrome children to leukemia

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Abstract

Rasha Awni Mohamed Guneidy, **The role of the glutathione and its related enzymes in the susceptibility of the Egyptian Down syndrome children to leukemia**.

Ph. D. Thesis: Biochemistry Department, Faculty of Science, Ain- Shams University.

This study was concerned with the examination of the level of the antioxidant enzymes, total glutathione (GSH) concentration and its related enzymes in the erythrocytes hemolysate of Down syndrome (DS), leukemia and DS-leukemia children as well as the normal children in order to investigate the possible variations as a function of DS and leukemia to obtain a comprehensive view of the leukemia patient antioxidant machinery in the Egyptian DS children. It was also concerned with the examination of the relationship between genetic polymorphism in GSTM1 and GSTT1 as well as characterization of the purified GST enzyme from normal and DS erythrocytes to illustrate the role of this enzyme in protection of the cell.

Blood samples were collected from the four groups for separation of leukocytes and erythrocytes.

All the levels of the tested enzymes in erythrocytes hemolysate of DS group were increased with the exception of GST and GSH concentration, while, their levels were decreased, except SOD in leukemia and DS-leukemia groups, compared with their levels in normal group.

Genomic DNA was extracted from leukocytes for determination of the frequencies of the GSTT1 and GSTM1 null genotypes. Genotype analysis of GSTT1 and GSTM1 indicated that, the incidences of GSTT1 null genotypes were 70% in DS patients compared to 90% in control group and 80% was the incidences of GSTM1 null genotypes in the two groups.

Polyacrylamide gel electrophoresis for the purified normal and DS erythrocytes GST indicated the presence of three bands with three different molecular weights, 35.5 kDa, 28 kDa and 23.2 kDa, respectively. The effect of freezing and thawing, storage time of freezing and GSH concentration on the stability of the purified enzyme from normal and DS erythrocytes indicated the sensitivity of normal GST enzyme compared to DS GST. On kinetic basis, DS GST differs from normal GST regarding Km, pH, activation energy, substrate specificity and the degree of inhibition. Also, with regard to stability, the individuals with lower overall GST activity and slight differences in some kinetic characters are at greater risk from xenobiotic contamination as compared to those with higher overall GST activity observed in normal individuals.

Key words: Down syndrome, antioxidants, oxidative stress, glutathione, leukemia, glutathione S-transferase, polymorphism.

Aim of work

To investigate the possible variations as a function of DS and leukemia to obtain a comprehensive view of the leukemia patient antioxidant machinery in the Egyptian DS children, this study was concerned with:

1- Examination of the level of the antioxidant enzymes, total glutathione (GSH) concentration and its related enzymes in the erythrocytes hemolysate of DS, leukemia and DS-leukemia children as well as the normal children.

2- Examination of the relationship between genetic polymorphism in GSTM1 and GSTT1 and the increased susceptibility to leukemia.

3- Characterization of the purified GST enzyme from normal and DS erythrocytes, illustrating the role of this enzyme in protection of the cell.

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List of Abbreviations

AD : Alzheimer disease

ALL : Acute lymphoblastic leukemia

AML : Acute myeloid leukemia

CAT : Catalase

CDNB : 1-chloro-2, 4- dinitrobenzene

CBB : Coomassie brilliant blue

DTT : Dithiotheritol

DS : Down syndrome

EDTA : Ethylene diaminetetraacetic acid

G-6-PDH: Glucose-6-phosphate dehydrogenase

GPx : Glutathione peroxidase

GR : Glutathione reductase

GSH : Reduced glutathione

GSSG : Glutathione disulfide (oxidized form)

GST : Glutathione *S*- transferase

GSTM1 : Glutathione *S*- transferase class mu

GSTT1 : Glutathione *S*- transferase class theta

Hb : Hemoglobin

HIV : Human immunodeficiency virus

IQ : Intelligence quotient

$NADP^+$: Nicotinamide adeninedinucleotide phosphate (Oxidized form)

NADPH : Nicotinamide adeninedinucleotide phosphate (Reduced form)

$O_2^{\bullet -}$: Superoxide radicals

$OH^{\bullet}$: Hydroxyl radical

PAGE : Polyacylamide gel electrophoresis

PCR : Polymerase chain reaction technique

ROS : Reactive oxygen species

SDS : Sodium dodecyl sulphate

SE : Standard error

SOD : Superoxide dismutase

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