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Blood Glutathione in Various Phases of Insulin-dependent Diabetes Mellitus in Children

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ABSTRACT

Reduced glutathione (GSH) in whole blood was studied in 15 insulin-dependent juvenile diabetic patients at onset of diabetes (group A). In 5 of these patients the blood GSH concentration was followed during the first month after onset. The blood GSH content was also analyzed in 16 children with insulin-dependent diabetes mellitus (IDDM) with a duration of diabetes of more than 2 years (group B), and in a control group of 76 healthy children (group C). The GSH levels in groups A, B and C were 48.3 ± 5.7, 47.1 ± 4.6 and 47.6 ± 4.3 mg/100 ml erythrocytes, respectively. Thus, there were no significant differences between the patients and the control group. In group A, there were no significant differences in blood GSH values at onset and 1 month later.

INTRODUCTION

Ever since Lazarow in 1949 launched his sulfhydryl (SH) theory for the pathogenesis of alloxan diabetes (9), there have been both experimental and clinical support for its validity, at least as it appears in a modified form (2, 10). The theory postulates that alloxan exerts its diabetogenic activity by forming irreversible compounds with glutathione (GSH) and other SH compounds, and that the insulin cells would be particularly sensitive to this SH reactivity because their GSH content would be at a more critical level than that of other cells. This, in turn, would be due to the fact that most of the SH-containing amino-acids (cysteine, methionine) are used for the insulin synthesis (the important SS-bridges of the molecule) and only little is left for the synthesis of GSH and other SH compounds (9). In the subsequent, slightly modified form, the theory postulates that alloxan essentially affects the SS-SH-compounds that are supposed to control the cell membrane permeability (2, 6, 10).

The main experimental support comes from Lazarow's (8) original observa-

tions that GSH protects against the diabetogenic activity of alloxan and that animals with a high blood GSH content, like guinea-pigs, are "alloxan resistant" (4). Moreover, alloxan induced a marked GSH decrease in the islet parenchyma, significantly more pronounced than in other solid tissues (3). Effects, similar to those of alloxan, can be obtained by administration of several different mono- and dithiol inhibitors, indicating that SH-reactive substances are potentially diabetogenic (6). Lastly, it has been shown that a putative imbalance in the islet SH content, either evoked by a cysteine deficiency (4) or by hypermethioninemia (1, 5), can be diabetogenic.

The clinical support is considerably weaker. It is, however, known that patients with persistant hypermethioninemia of familial type have insulin cell hyperplasia, hyperinsulinemia and hyperglycemia (11). In homocystinuria patients, who besides homocystinemia, also have hypermethioninemia, both hyperglycemia and decreased serum insulin concentrations have been observed (7).

Against this background we have tested the SH hypothesis in children with IDDM. This was done both at onset of their diabetes, and in an IDDM group with a duration of diabetes of more than 2 years, as well as in a control group of children.

PATIENTS

The patients and their healthy controls were assigned to the following groups:

A: A group of 15 IDDM patients, 2-12 years of age, in whom blood samples for GSH were collected before the institution of insulin therapy. In 5 of these patients, blood samples were also collected 1 month after the start of the insulin therapy.

B: A group of 16 IDDM patients, 4-18 years of age, with a duration of diabetes of 2-14 years.

C: A control group of 76 healthy children, 4-16 years of age.

METHODS

The hematocrit value was obtained on capillary blood after conventional centrifugation.

GSH was analyzed within 5 hrs after blood collection by the orthophthal-aldehyde (OPT) method, according to Havu (6).

RESULTS AND DISCUSSION

The GSH concentration per 100 ml red blood corpuscles (RBC) was 48.3 ± 5.7 mg in group A before insulin treatment. The blood GSH in 5 individual samples from patients in group A before, and 1 month after, the introduction of insulin therapy showed no significant changes.

In group B the GSH concentration was 47.1 ± 4.6 mg/100 ml RBC and among the healthy children (group C) 47.6 ± 4.3/100 ml RBC. Thus, there was no statistically significant difference between these two groups or between the control group and the group of children with newly diagnosed diabetes (Table 1).

Table 1. GSH concentration in erythrocytes (mean ± SE) in newly diagnosed insulin-dependent diabetic children at onset and after 1 month of insulin therapy; in a retrospective diabetic children group and in healthy controls.

	DIABETICS			CONTROLS
	Time after onset			
	A)	A)	B)	C)
	0-12 hours	1 month	2-14 years	
GSH-concentration/ 100 ml red blood corpuscles	48.3 ± 5.7	47.6 ± 4.4	47.1 ± 4.6	47.6 ± 4.3
	n = 15	n = 5	n = 16	n = 76

A) Prospective diabetic patient group
B) Retrospective diabetic patient group
C) Control group

Although there is normal blood GSH in diabetic patients, it might still be some error in the SH balance in diabetic patients, but this error might then be closer to the target organ, i.e. in the insulin cells. Admittedly, no GSH determinations of islet-cell tissue in diabetic patients have been performed, so far.

From our previous experimental studies (3) we know that the erythrocyte GSH may have returned to normal while the islet GSH is still significantly lowered. Thus, the present study has confirmed the suspicion that GSH-analyses of RBC are rather non-informative.

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