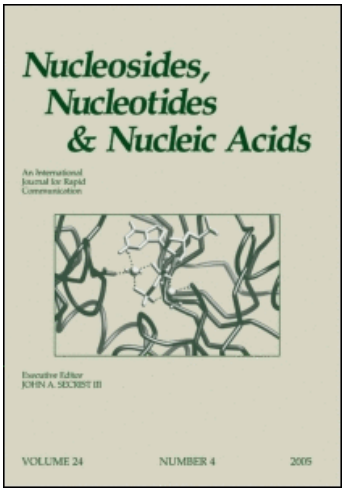

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A PIVOTAL ROLE FOR β-AMINOISOBUTYRIC ACID AND OXIDATIVE STRESS IN DIHYDROPYRIMIDINE DEHYDROGENASE DEFICIENCY?

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□ *Dihydropyrimidine dehydrogenase (DPD) constitutes the first step of the pyrimidine degradation pathway in which the pyrimidine bases uracil and thymine are catabolised to β-alanine and β-aminoisobutyric acid (β-AIB), respectively. The mean concentration of β-AIB was approximately 5- to 8-fold lower in urine of patients with a DPD deficiency, when compared to age-matched controls. Comparable levels of 8-hydroxydeoxyguanosine (8-OHdG) were present in urine from controls and DPD patients at the age < 2 year. In contrast, slightly elevated levels of 8-OHdG were detected in urine from DPD patients with an age > 2 year, suggesting the presence of increased oxidative stress.*

Keywords Dihydropyrimidine dehydrogenase; β-Aminoisobutyric acid; 8-Hydroxydeoxyguanosine; Oxidative stress

INTRODUCTION

In man, the pyrimidine bases uracil and thymine are degraded via a 3-step pathway. DPD is the initial enzyme, catalysing the reduction of thymine and uracil to 5,6-dihydrothymine and 5,6-dihydrouracil, respectively. The second step consists of a hydrolytic ring opening of the dihydropyrimidines which is catalyzed by dihydropyrimidinase. Finally, the resulting N-carbamyl-β-aminoisobutyric acid and N-carbamyl-β-alanine are converted in the third step to β-AIB and β-alanine, ammonia and CO_2 by β-ureidopropionase. It has been shown that in patients with a DPD deficiency, the levels of β-AIB were strongly decreased or even undetectable in plasma.[1] In contrast, only a moderately decreased concentration of β-AIB was detected in urine

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from DPD patients.[1] In 2 patients with a β-ureidopropionase deficiency, strongly elevated levels of 8-OHdG were observed, indicating the presence of increased oxidative stress.[2] In this study, we investigated the levels of β-AIB in DPD patients of 2 different age groups and whether these DPD patients suffered from oxidative stress.

MATERIALS AND METHODS

The concentration of β-AIB in urine was determined with a dual-column reversed-phase HPLC procedure, combined with fluorescence detection of the orthophthaldialdehyde derivatives.[1] 8-OHdG in urine was measured using reversed-phase HPLC with electrochemical detection.[2] Differences between the mean concentrations of β-AIB and 8-OHdG between patients and controls were analyzed with the nonparametric Mann-Whitney test.

RESULTS

The mean concentration of β-AIB was approximately 5-fold decreased in urine from DPD patients with an age <2 year and 8-fold decreased in urine from DPD patients with an age >2 year, when compared to age-matched controls (Table 1). In general, the mean concentration of β-AIB was higher in the age group of 0–2 year when compared to the group with an age >2 year. To investigate whether patients with a DPD deficiency suffer from increased oxidative stress, the levels of 8-OHdG were measured in urine (Figure 1). Normal concentrations of 8-OHdG were present in the urine from DPD patients with an age <2 year, compared to age matched controls. However, the mean concentration of 8-OHdG was increased in the urine from DPD patients >2 year (Table 1). In the case of a child suffering from an anaplastic large cell lymphoma and a DPD deficiency, a very high concentration of 8-OHdG was detected in urine (28 nmol/mmol creatinine).

DISCUSSION

The levels of β-AIB in urine proved to be higher in controls and DPD patients in the age group 0–2 year when compared to those with an age >2 year. Nevertheless, the impaired degradation of thymine in patients with a DPD deficiency resulted in strongly decreased levels of β-AIB in urine of all DPD patients. β-AIB is a structural analogue of γ-aminobutyric acid and glycine, which are the major inhibitory neurotransmitters in the central nervous system. In addition, β-AIB has been shown to be a partial agonist of the glycine receptor. Thus, the altered homeostasis of this β-amino acid,

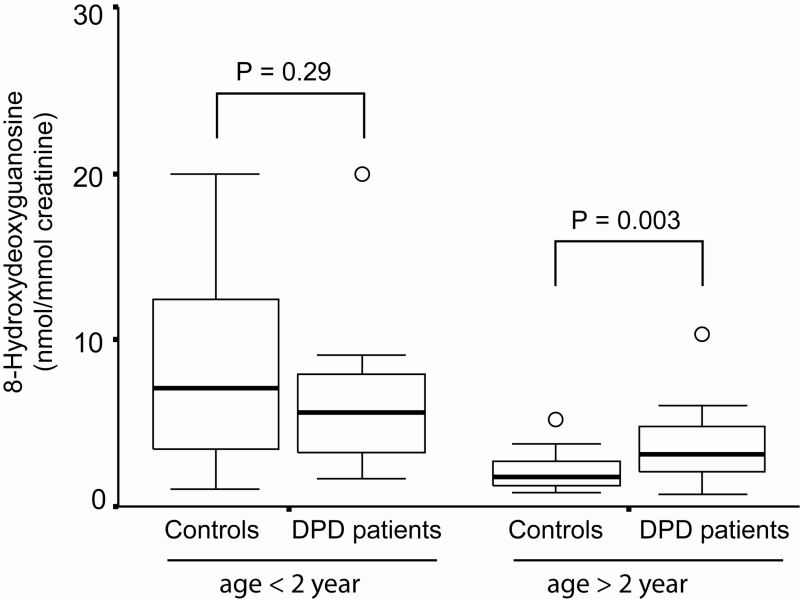

FIGURE 1 Box plots of the 8-OHdG concentrations in controls and DPD patients. The top, bottom, and line through the middle of a box correspond to the 75th percentile, 25th percentile, and 50th percentile, respectively. The whiskers on the bottom extend from the 5th percentile and top 95th percentile. The open circles represent outliers.

as observed in patients with a DPD deficiency, might underlie some of the neurological abnormalities encountered in these patients.

8-OHdG originates from the oxidation of guanine in DNA and upon DNA repair, 8-OHdG is excreted in the urine. The urinary level of 8-OHdG

TABLE 1 Levels of β-AIB and 8-OHdG in Urine of Controls and DPD Patients

	DPD patients	Controls	*P*
Age <2 year			
8-OHdG[a]			
Mean ± SD	6.4 ± 4.8 (n = 13)	8.5 ± 5.8 (n = 40)	0.29
Range	1.7–20	1.0–20	
β-AIB[b]			
Mean ± SD	5.4 ± 5.9 (n = 12)	24.2 ± 13.8 (n = 12)	<0.001
Range	0.5–17.3	4.4–50.0	
Age >2 year			
8-OHdG[a]			
Mean ± SD	3.6 ± 2.3 (n = 16)	2.0 ± 1.0 (n = 34)	0.003
Range	0.7–10.3	0.8–5.2	
β-AIB[b]			
Mean ± SD	1.3 ± 1.6 (n = 20)	10.6 ± 7.8 (n = 27)	<0.001
Range	0.10–7.3	0.60–31.4	

[a]nmol/mmol creatinine. [b]μmol/mmol creatinine.

is considered to be a marker of generalized, cellular oxidative stress.[3] In DPD patients, with an age >2 year, the elevated urinary levels of 8-OHdG compared to age-matched controls, indicate that they are suffering from increased oxidative stress. The very high levels of 8-OHdG in a child suffering from an anaplastic large cell lymphoma and a DPD deficiency is in agreement with the fact that malignant cells contain high levels of oxidised DNA lesions and that high 8-OHdG levels have been found in urine from patients with tumors.[3]

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