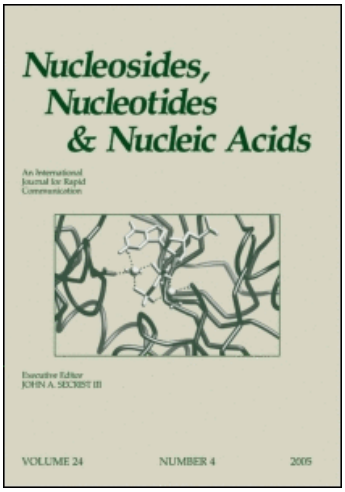

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AMPD1 C34T MUTATION SELECTIVELY AFFECTS AMP-DEAMINASE ACTIVITY IN THE HUMAN HEART

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▫ *Possession of the nonsense mutation in AMPD1 C34T gene has been linked to improved survival in patients with heart failure, possibly by promoting the formation of adenosine. This mutation is known to decrease the activity of AMP-deaminase in skeletal muscle. We have found that the AMPD1 mutation decreases the activity of AMP-deaminase in the heart without changing the activity of any other enzymes of adenine nucleotide metabolism. Protective mechanism of this mutation may be thus induced by local cardiac metabolic changes.*

Keywords AMP-deaminase, C34T Mutation, Human Heart, Adenosine

INTRODUCTION

An improved prognosis in heart failure was described in subjects with the C34T (Glu12Stop) nonsense mutation of the *AMP-deaminase 1 (AMPD1)* gene.[1,2] This gene is predominantly expressed in skeletal muscle and possession of this mutation leads to decreased activity of AMP-deaminase and the accumulation of cytoprotective adenosine in skeletal muscle. However, little is known about the metabolic changes within the heart; in this study we evaluated the effect of the C34T mutation on cardiac enzymes involved in adenosine metabolism.

MATERIALS AND METHODS

Screening for *AMPD1* genotype and measurement of enzyme activities was performed on 27 patients with end-stage heart failure at the time of transplantation or left ventricular assist device (LVAD) implantation. The presence of the C34T

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TABLE 1 Enzyme Activities in Human Cardiac Biopsies

	C/C	C/T
AMP-deaminase (AMPD)	1.06 ± 0.09	0.59 ± 0.02*
Ecto-5′-nucleotidase (E5′N)	4.60 ± 0.42	3.96 ± 0.41
Purine nucleoside phosphorylase (PNP)	0.98 ± 0.07	1.03 ± 0.21
Adenosine deaminase (ADA)	0.41 ± 0.04	0.36 ± 0.02
Adenosine kinase (AK)	0.016 ± 0.002	0.018 ± 0.002

Results are expressed as mean activities μmol/min/g wet weight ± SEM. *p = 0.003, C/C vs. C/T.

mutation was assayed by single-stranded conformational polymorphism (SSCP) and restriction-fragment length polymorphism (RFLP) on extracted DNA. Cardiac specimens were homogenized and assayed for AMP-deaminase, ecto-5′-nucleotidase (E5′N), purine nucleoside phosphorylase (PNP), adenosine deaminase (ADA), and adenosine kinase (AK). Enzyme activities were analyzed by measuring the conversion of substrates into product by HPLC.[3]

RESULTS AND DISCUSSION

AMP-deaminase activity in heterozygous (C/T) individuals was 45% of that found in normal wild-type (C/C) individuals. There were no significant differences in activities of any other enzymes when C/T was compared to C/C individuals, for E5′N, PNP, ADA, or AK (Table 1).

We have shown for the first time a correlation between the *AMPD1* mutation and attenuated AMP-deaminase activity in the heart, therefore potentially promoting cardioprotection in a localised manner. These changes did not affect any other enzyme involved in adenosine/nucleotide metabolism. Decreased cardiac activity of AMP-deaminase, potentially leading to increased adenosine production, could be responsible for protective effects of this mutation observed in patients with heart disease.

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