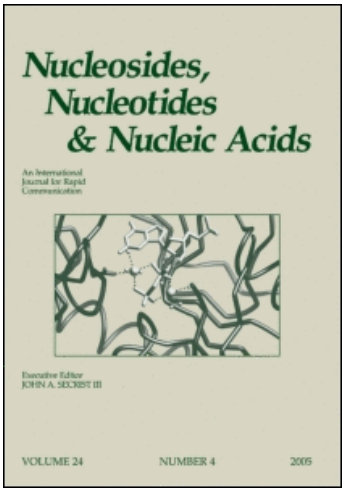

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URINARY GUANIDINOACETATE AND CREATINE LEVELS IN PATIENTS WITH HPRT DEFICIENCY

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□ *Neurobehavioral manifestations of complete HPRT deficiency include severe action dystonia, choreathetosis, alteration of executive functions, and self-injurious behavior. Dystonic manifestations are also present in patients with partial HPRT deficiency. Pathophysiology of these manifestations is unknown. Guanidinoacetate is a neurotoxin implicated in certain dystonic syndromes. We have examined guanidinoacetate and creatine levels in urine from 11 HPRT deficient patients (9 with Lesch-Nyhan syndrome and 2 with partial deficiency). Urinary guanidinoacetate and creatine levels in HPRT deficient patients were within the normal range. Guanidinoactetate alteration does not seem to be implicated in the pathogenesis of the neurological disease associated with HPRT deficiency.*

Keywords Lesch-Nyhan syndrome; HPRT; dystonia; guanidinoacetate; creatine

INTRODUCTION

The neurobehavioral manifestations of complete HPRT deficiency or Lesch-Nyhan syndrome (OMIM 300322) include: severe action dystonia, choreathetosis, alteration of executive functions, and self-injurious behavior.[1] Partial HPRT deficiency (OMIM 300323) is also associated in many cases with less severe dystonic signs. The pathophysiology of these neurological manifestations in HPRT deficiency is unknown, although the alteration of dopaminergic neurotransmission is the most accepted hypothesis. Guanidinoacetate, a metabolite of the creatine synthesis pathway, may behave as a neurotoxin, and has been implicated in dystonic syndromes.[2,3] The enzyme guanidinoacetate-methyltransferase, with S-adenosylmethionine as methyl group donor, catalyzes synthesis of creatine and S-adenosylhomocysteine. Depletion of adenine nucleotides (e.g.,

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ATP) has been proposed as a potential mediator in the pathogenesis of Lesch-Nyhan syndrome.[4] An isolated observation in a Lesch-Nyhan syndrome patient showed that S-adenosylmethionine administration caused a significant reduction in self-injury and dystonic symptoms.[5] We, thus, hypothesized that a S-adenosylmethionine defect could produce a decrease of creatine synthesis and an excess of guanidinoacetate, which might in turn contributed to the development of some of the neurological manifestations of HPRT deficiency.

PATIENTS AND METHODS

Patients

We examined urinary excretion of creatine and guanidinoacetate in 11 HPRT deficient patients (9 with Lesch-Nyhan syndrome and 2 with partial HPRT deficiency).[6] Deficiency of HPRT was diagnosed based on the following: a) clinical symptoms and signs typical of an HPRT-deficient state; b) biochemical abnormalities consistent with this diagnosis; c) deficiency of HPRT activity; and d) molecular genetic testing. All patients were treated with allopurinol to normalize urinary and serum uric acid levels. The urine sample was maintained at –20°C until assay.

Methods

Guanidinoacetate and creatine were determined by isotope dilution tandem mass spectrometry.[7]

TABLE 1 Urinary guanidinoacetate, creatine, and creatine/creatinine ratio in HPRT deficient patients

Patient	Guanidinoacetate (mmol/L)	Creatine (μmol/L)	Creatine/Creatinine ratio
Control range	<12 y: 13–139 >12 y: 12–97 >12 y: 12–97	12-9490	0.01–1.51
LN1	106	289	0.03
LN2	103	779	0.37
LN3	30	265	0.03
LN4	38	168	0.05
LN5	65	1241	0.35
LN6	56	4474	0.59
LN7	84	712	0.19
LN8	77	4032	0.55
LN9	107	1897	0.42
P1	54	3181	0.51
P2	13	95	0.02

LN: Lesch-Nyhan disease; P: partial HPRT deficiency.

RESULTS

Urinary levels of guanidinoacetate and creatine and creatine/creatinine ratio levels in HPRT deficient patients were found to be within the range found in normal individuals (Table 1).

CONCLUSION

Guanidinoacetate excretion is not increased in patients with HPRT deficiency. Therefore guanidinoacetate does not appear to be implicated in the pathogenesis of the neurological disease associated to HPRT deficiency.

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