Acetoacetate Does Not Prevent Maleate-induced Proteinuria in Rats

O.W.

Otto W.

Neuhaus

Department of Biochemistry, University of South Dakota School of Medicine, Vermillion, S. Dak., USA

Otto W. Neuhaus, PhD, Department of Biochemistry, University of South Dakota School of Medicine, 414 E. Clark, Vermillion, SD 57069-2390 (USA)

Dear Sir,

Sodium maleate has been used to create and study renal tubular dysfunction comparable to Fanconi's syndrome [1]. This compound forms maleyl-CoA by reacting with succinyl-CoA (succinyl-CoA transferase), thereby reducing the cellular CoA supply and inhibiting the citric acid cycle [2]. The resulting reduced ATP supply or the reaction of the maleyl-CoA with proteins (membrane) may inhibit a variety of renal transport systems, resulting in phosphaturia, glucosuria, aminoaciduria, ketonuria and also proteinuria. Acetoacetate, the normal substrate for succinyl-CoA transferase, prevents the maleate-induced tubular dysfunction of Na⁺-dependent transport systems but does not restore cellular ATP [3]. Maleyl-CoA, not the reduced ATP level, may be responsible for 'most if not all' renal effects of maleate [3, 4].

Protein reabsorption may be influenced by maleate for reasons independent of the transport of metabolites. Maleate blocks both the tubular endocytotic process as well as the vesicular transport of proteins within cells [5]. It has been suggested that maleate causes proteinuria by inhibiting ATP production but no evidence was offered [6]. No apparent effort has been made to date to use acetoacetate to test the potential reversibility of the action of maleate on protein reabsorption. If the inhibition of protein reabsorption is caused by low ATP levels and not a direct effect of maleyl-CoA, then acetoacetate should have no effect on the maleate-induced proteinuria. The current communication shows that this is indeed the case; acetoacetate does not reverse the maleate-induced effect on the reabsorption of the low molecular weight protein of adult male rats, α_2 -globulin.

U—i—γ

-40 -20 0 20 40 60 80 100 120

Time, min

-40 -20 0 20 40 60 80 100 120 140 Time, min

Fig. 1. Experiments were performed in which maleate (150 mg/kg) was injected with (—) and without (---) acetoacetate in the perfusion medium; a Data for glucose (n = 6); b data for c_{1/8}-globulin (n = 3–6). Abscissa values represent 20-min collection periods; ordinate values are excretion rates (μg/min) for glucose (a) or c_{1/8}-globulin (b).

Experiment

Adult male Sprague-Dawley rats (275–300 g) were infused intravenously with a mildly diuretic Krebs-Ringer buffer as described previously [7]. Twenty-minute urine samples were collected

from a bladder catheter. Assays for α_2 -globulin were made using a radial immunodiffusion process [7]. Glucose was measured using a quantitative, enzymatic method (Sigma). At t_0 , sodium maleate was injected as a single bolus (150 mg/kg). In appropriate studies, acetoacetate (200 mg, pH 3.5) was included in the infusion medium [3].

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As seen in figures 1a and b, maleate caused an increase 2 in urinary excretion rate for both glucose and α_2 -globulin. Although infusion with acetoacetate completely eliminated the glucosuria (fig. 1a), it had no effect on the proteinuria (fig. 1b).

It is assumed that sodium maleate effects the endocytic uptake of α_2 -globulin either by the depression of cellular ATP levels or by effects caused by maleyl CoA. Evidence presented here indicates that acetoacetate reverses the maleate-induced inhibitory effect on glucose transport, as expected, but exerts no influence on the renal uptake of α_2 -globulin. It is suggested, therefore, that maleate affects protein reabsorption as a consequence of the lowered cellular ATP levels [6].

7 Acknowledgment

This study was supported by grants from the Parsons Endowment Fund, USD School of Medicine, and the Fraternal Order of the Eagles. The author is especially grateful to Susan Tiaht for technical assistance and to Dr. Craig Piquette who initiated this study while working in the author's laboratory.

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