The Role of Magnesium in the Pathogenesis of Azotemic Hypothermia (35729)

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(Introduced by W. R. Wilson)
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Hypermagnesemia has been observed in patients with uremia, since 1934 when Hirschfelder pointed out the dangers of Epsom salt purgation in patients with nephritis (1). It has been subsequently demonstrated that the hypermagnesemia associated with uremia is primarily due to decreased urinary excretion of this cation (2, 3). Another manifestation of uremia is decreased body temperature. This aspect of renal failure was mentioned by Bourneville in 1873 (4), and hypothermia due to experimental uremia was reported in 1892 (5). The clinical importance of uremic hypothermia was stressed by Schreiner and Maher (6) in their monograph on uremia. The cause of uremic hypothermia, however, is still unknown.

In this study, we investigated hypermagnesemia as the potential cause of uremic hypothermia. Was there any reason to suspect this possibility, aside from the fact that hypermagnesemia is common in uremia? We believe so. Hypermagnesemia has been observed in a number of hibernating animals, *i.e.*, groundhog (7), hedgehog (8), bat (9), and ground squirrel (10). Furthermore, the parenteral injection of magnesium salts in both rabbits and dogs leads to decreased body temperature (11, 12). Finally, it has been suggested that the antipyretic effects of salicylic acid may be due to increased blood magnesium (13).

The questions investigated were: (1) Does azotemia produced by ureteral ligation lead to hypothermia in the rat? (ii) Is azotemic hypothermia accentuated by hypermagnesemia? (iii) Does azotemic hypothermia occur in the absence of hypermagnesemia?

Methods. Forty female Sprague-Dawley rats weighing approximately 200 g, were randomly divided into control and test groups. The animals were pair fed a synthetic casein-base diet containing negligible amounts of sodium, potassium, magnesium, chloride, and phosphorus. Electrolytes were provided in a gavage solution by means of an automatic refilling syringe pipet; each 5 ml contained 1.25 mEq of Na, 2 mEq of K, 2.5 mEq of Cl, 1.25 mEq of Mg, and 0.75 m*M* P. Magnesium was eliminated from the gavage solution of the test animals (groups III and IV). Deionized water was allowed *ad libitum.*

The rats were put in individual metabolic cages. Urine was collected on the sixth and seventh days of the experiment. The urine was acidified by 1% vol HCl and diluted with water to predetermined volume. On the eighth day, the rats were anesthetized with ether and a surgical procedure was performed under sterile conditions. The lower abdomen was entered, the bladder was identified and retracted. The bladder was either ligated at the base (Groups I and III), or not ligated (Groups II and IV).

Following the surgical procedure, all rats were fasted but allowed water *ad libitum.* Temperature was determined before surgery and 12 hr later at the time of sacrifice. Rectal temperatures were measured with an electric thermistor probe. The rats were exsanguinated under ether anesthesia by puncture of the abdominal aorta, using a 19-gauge needle with attached plastic tubing. Blood was

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TABLE I. Influence of Ureteral Ligation on Plasma Chemistries and Rectal Temperatures.[a]

Magnesium intake:	Normal		Low	
Group:	I	II	III	IV
	Ureteral ligation	Sham operation	Ureteral ligation	Sham operation
No. of animals:	(9)	(8)	(9)	(8)
Plasma				
Urea nitrogen (mg/100 ml)	101 ± 6	29 ± 2	102 ± 3	27 ± 2
Magnesium (mEq/liter)	3.41 ± 0.15	1.92 ± 0.07	1.29 ± 0.06	1.28 ± 1
Sodium (mEq/liter)	137 ± 3	140 ± 1	140 ± 2	141 ± 1
Potassium (mEq/liter)	7.7 ± 0.3	3.9 ± 0.1	6.9 ± 0.3	3.8 ± 0.1
Phosphorus (mg/100 ml)	13.9 ± 0.6	6.3 ± 0.2	14.1 ± 0.3	5.9 ± 0.2
Urine				
Phosphorus (mg/48 hr)	27.4 ± 0.7		38.6 ± 1.4	
Temp (°)				
Before surgery	38.5 ± 0.1	38.6 ± 0.1	38.3 ± 0.1	38.5 ± 0.1
12 hr after surgery	33.8 ± 0.4	38.1 ± 0.1	35.1 ± 0.2	37.9 ± 0.2

			p		p		p
	UN	I vs II	$<.001$	I vs III	$>.1$	II vs IV	$<.001$
	Mg	I vs II	$<.00$	I vs III	$<.001$	II vs III	$<.001$
	K	I vs II	$<.001$	I vs III	$<.05$		
Plasma	P	I vs II	$<.001$	I vs III	$>.1$	II vs IV	$<.001$
Temp		I vs II	$<.001$	I vs III	$<.02$	II vs III	$<.001$

[a] All values are means ± $SE_{\bar{x}}$.

allowed to flow freely into a heparinized centrifuge tube until respiration ceased. Blood was mixed, centrifuged, and the plasma was removed from the red cells within 1 hr.

Magnesium was measured on the AutoAnalyzer, using the colorimetric reaction with Eriochrome black T (14); sodium and potassium by internal standard flame photometry; blood urea nitrogen by the AutoAnalyzer method, using colorometric reactions with diacetyl monoxime; and inorganic phosphate by the AutoAnalyzer colorimetric phosphomolybdic reaction. Statistical methods included the standard Student's t test (15).

Results. The results are summarized in Table I and Fig. 1. Both groups of ureterally ligated rats were azotemic, hyperkalemic, and hyperphosphatemic to a significant degree when compared to their sham-operated controls. There was no significant difference between the plasma urea nitrogen and plasma phosphorus between Groups I and III, however. The plasma potassium was different at the 5% level. The plasma magnesium in the sham-operated rats on a normal magnesium intake (Group II) was 1.92 mEq/liter, a value comparable to that observed by other investigators (16, 17). As anticipated, the plasma magnesium of the Group I ligated rats (3.41 mEq/liter) was significantly higher than in the Group II sham-operated control rats ($p<.001$). Both magnesium-restricted groups of rats had plasma magnesium values below normal; there was no difference in the plasma magnesium between the Group III ligated and the Group IV sham-operated rats.

The mean temperature of the Group II sham-operated control rats was 38.1°. The Group I hypermagnesemic, azotemic rats had mean temperature values significantly less than this (33.8°, $p<.001$). The Group III azotemic rats, without magnesium retention, demonstrated a mean temperature which was intermediate between the two values noted above (35.1°). Although less than observed in the sham-operated controls (38.1 vs 35.1, $p<.001$), it was not as low as observed in the Group I hypermagnesemic rats (33.8 vs 35.1, $p<.02$). Finally, there was no significant difference between the temperature of the Group

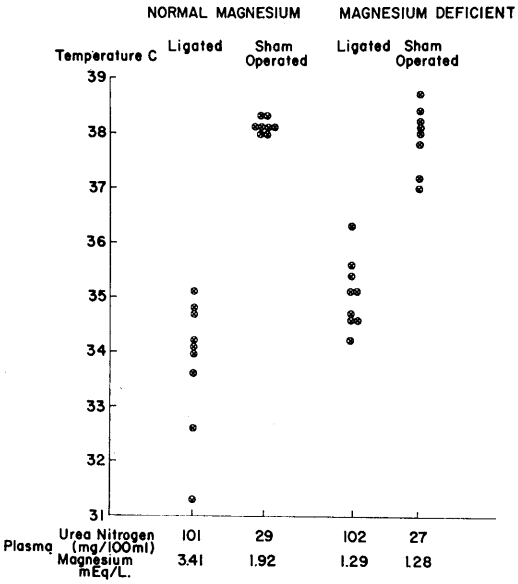

FIG. 1. Influence of plasma magnesium on body temperature in azotemic rats. Note that although the temperature was lowest in the hypermagnesemic azotemic rats, the azotemic rats on magnesium-deficient diets also showed temperature values less than observed in sham-operated controls.

II sham-operated rats on normal magnesium intake and the Group IV sham-operated rats which were magnesium depleted. Hypomagnesemia alone therefore had no influence on body temperature in this particular experiment.

Discussion. As anticipated, azotemia in the rat is characterized by a body temperature which is less than normal. The hypothermia was clearly evident within 12 hr after the ureteral ligation. Furthermore, the decrement in body temperature was most striking in those rats which were also hypermagnesemic. This observation was not surprising since an interrelationship between magnesium and body temperature has been observed in a variety of animals (7–12).

Although the body temperature was lowest in the hypermagnesemic rats, magnesium retention is not essential to the development of azotemic hypothermia. The influence of ureteral ligation on body temperature in the magnesium-deficient rats is seen in Fig. 1. Each of the nine ligated Group III rats had temperatures less than that observed in the sham-operated controls despite hypomagnesemia. Although hypermagnesemia accentuates azotemic hypothermia, this effect was minor, and magnesium is clearly not the most important factor involved in the pathogenesis.

This study does not therefore determine which factors are critical to the development of azotemic hypothermia. In 1924, Mozer (18) reviewed some clinical evidence associating hypothermia with azotemia *per se*. He furthermore observed that in rabbits, the injection of a relatively pure source of urea alone produced hypothermia. However, the dose had to exceed 4 g daily to obtain this effect.

Urea is not the only agent which has been incriminated. In 1958, Feher *et al.* (19) isolated a substance from the blood of uremic dogs which was hypothermic in rats and which they believed to be a peptide. This substance was not a product from a diseased kidney since it appeared in the blood of a nephrectomized animal as well.

In summary, multiple factors appear to be involved in the pathogenesis of azotemia hypothermia. Magnesium appears to be one of these, albeit, a nonessential one.

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