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THE EFFECT OF AMINO ACIDS ON SERUM AND URINE CREATINE

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There is now unequivocal evidence that creatine is formed from glycine, arginine, and methionine (1). It is equally well established that creatine can be transformed into creatinine and excreted in this form by the kidneys (2). Creatine is also concerned with the intermediary metabolism of carbohydrate.

By a photometric modification of Folin's method, devised by Peters (3), Tierney and Peters (4) demonstrated that the serum of normal men contained measurably significant amounts of creatine. They found that the serum creatine was elevated in patients with hyperthyroidism. Creatinuria was almost invariably associated with concentrations of serum creatine greater than 0.6 mgm. per cent, suggesting that creatine, presumably filtered in the renal glomeruli, is completely reabsorbed in the tubules when its concentration in the serum is less than 0.6 mgm. per cent.

The present paper deals with the serum creatine and creatine excretion in various pathological conditions and after certain induced physiological disturbances.

METHODS

Patients on the wards of the New Haven Hospital were studied. Serum from blood collected under oil and centrifuged with anaerobic precautions was analyzed by the method described by Peters (3). Specimens of urine were collected whenever possible during the course of the experiments and analyzed by a similar method, using the suggestion of Tierney and Peters (4) that the urine be diluted to a specific gravity of 1.010. It was found that if 5 ml. of urine, already diluted to a specific gravity of 1.010, were further diluted to 200 ml., the concentration of creatine more regularly fell into a range suitable for photometric measurement.

All experiments were conducted in the morning, after patients had been without food for 10 hours or more. No food was given until the experiments were completed, except in the 2 instances in which the effects of large meals were observed. For the glucose studies, 50 ml. of 50 per cent glucose were injected intravenously. In other experiments, 50 grams of an enzymatic hydrolysate of casein (Amigen, made by Mead, Johnson and Co.) were injected intravenously, either as a 10 per cent solution or as a 5 per cent solution in 5 per cent glucose. This contains 6 grams of nitrogen. Blood samples were collected before the injection, 5 minutes after the termination of the infusion, and at intervals thereafter. Samples were never taken from the vein used for the infusion. All determinations were made in duplicate and, if these did not check, were repeated or discarded. Changes of serum creatine smaller than 0.2 mgm. per cent are not considered significant.

RESULTS

In Table I are observations on 26 men and 13 women with various diseases. Of the men, only 7 had creatinuria, and in all of these, serum creatine exceeded 0.7 mgm. per cent. SP had no creatinuria during the experiment although his serum creatine was 1.62 mgm. per cent. Creatine did, however, appear in his urine later in the day. This unusual sequence may have been related to renal failure which Rabe (5) has found may disturb the relations between urine and serum creatine in bizarre ways. Women had creatinuria more frequently than men, but only when the serum creatine exceeded 0.5 mgm. per cent. No creatine was found in the urine of MP with a serum creatine of 0.7 mgm. per cent. It is to be noted that on several occasions no significant amount of creatine could be demonstrated in the serum.

With the exception of JCo, all the men with elevated serum creatine were desperately ill; in fact all of them died within 5 days of the observations. This was not true of the women, although the prognosis in the cases of RF, GM, and DB was considered poor or hopeless. This is merely another illustration of the greater tendency to creatinuria among women.

Table II shows the effects on serum and urine creatine of a meal, intravenous glucose, and intravenous casein hydrolysate. Neither the meals nor the glucose infusions altered serum creatine. In the experiment in which urine was obtained

TABLE I

Urine and serum creatine in miscellaneous diseases

Subject	Creatine		Diagnosis
Male	Serum	Urine[1]	
	mgm. per cent	*mgm. per cent*	
JCo	0.8	27	Fractures of ribs and legs
HC	0.2	0	Regional enteritis
PO	0.7	0	Carcinoma of stomach
HM	0.3	0	Lymphosarcoma
EM	0.1	0	Peptic ulcer with obstruction
CL	0.2	0	Reticulum cell sarcoma
CV	0.1	0	Pernicious anemia
EC	0.2	0	Pernicious anemia
FC	0.3	0	Carcinoma of lung w/ metastases
AS	0.5	0	Carcinoma of lung w/ metastases, jaundiced
ED	0.2	0	Postoperative appendectomy
RS	0	0	Postoperative appendectomy
VP	0.3	0	Postoperative appendectomy
HD	0.3	0	Osteomyelitis of jaw
AG	0.3	0	Empyema
FD	0.1	0	Meningococcus meningitis
JSa	0.1	0	Advanced pulmonary tuberculosis
JCa	1.4	44	Far advanced pulmonary tuberculosis, died[2]
TE	1.2	16	Tuberculosis with tuberculous meningitis, died[2]
LP	0	0	Undiagnosed muscular disease, ? dermatomyositis
GC	0.2	0	Myasthenia gravis, treated
SP	1.6	0[3]	Bronchopneumonia, died[2]
JSi	2.0	46	Bronchopneumonia, died[2]
CP	2.6	117	Subacute bacterial endocarditis, died[2]
FL	1.4	53	Syphilis, subarachnoid hemorrhage, died[2]
BB	1.3	23	Regional enteritis, died[2]
Female			
AH	0	0	Pernicious anemia of pregnancy
FH	0.5	0	Diabetes, psychoneurosis
HF	0.5	0	Diabetes, gangrene of foot
MJ	0.3		Diabetes, post-acidosis
LD	0.3	0	Acute rheumatic fever with carditis and failure
AR	0.6	29	Acute rheumatic fever with carditis and failure
ET	0.5	8	Heart disease with fibrillation and failure
MF	1.2	8	Hypertensive cardiovascular disease and failure
MP	0.9	19	Ulcerative colitis
	0.7	0	
DB	0.9	25	Cerebral thromboses
RF	0.6	11	Chronic febrile disease, ? lupus
GM	0.9	84	Disseminated lupus
AC	1.0	7	Acute trichiniasis

[1] Concentration in urine diluted to 0.010.
[2] All patients who died did so within 5 days of study.
[3] NPN elevated to 57.

before and after glucose (SP), the rate of creatine excretion did not change.

The response to intravenous casein hydrolysate depended on the initial concentration of creatine in the serum. In the 4 patients with normal values before infusion, serum creatine remained within normal limits after infusion, although its concentration varied slightly. These variations

TABLE II

The effects of various procedures upon urine and serum creatine

Hours are counted from the end of the infusions or meals. *Start* indicates the initial post-absorptive value. The infusions of casein hydrolysate were given over periods of 2 hours or more. Consequently, values are given not only at the start, but also at the end of the infusion. Urine figures in parentheses represent concentrations of creatine in terms of mgm. per cent, when the rate of urine excretion could not be determined because the period over which it was formed is unknown. Clearances are estimated only over periods in which the concentration of creatine in the serum remained constant (post-absorptive specimens) or when it was descending. In the latter case, it was calculated by the method described by Winkler and Parra (7).

Subject	Time	Creatine		
		Serum	Urine	Clearance
	hours	*mgm. per cent*	*mgm. per hour*	*ml. per min.*
Infusions of casein hydrolysate				
CP	Start	2.3	86	63
	End	2.7		
	1	2.6	40	
	2	2.3		
	3	2.2	120	
	4	2.2		
	5		157	120
GM	Start	0.9	(30)	
	End	1.5		
	1	1.1	74	
	2	0.9		
	3	0.8	37	65
	4	0.7		
	5		10	24
DB	Start	0.9	22	44
	End	1.5		
	2	1.1	43	
	4	1.0	29	47
JS	Start	2.0	(83)	
	End	3.4		
	1		(125)	
	4	3.4		
	6		14	7
SP	Start	1.6	0	0
	End	2.3	0	
	2	2.3		
	4	1.0	26	
	6		26	43
BB	Start	1.3	15	21
	During	1.5	35	
	End	1.5	13	
	2	1.0		
	5		4	

TABLE II—*Continued*

Subject	Time	Creatine		
		Serum	Urine	Clearance
	hours	*mgm. per cent*	*mgm. per hour*	*ml. per min.*
Infusions of casein hydrolysate—*Continued*				
RF	Start	0.6	(13)	
	End	0.6		
	2	0.4	10	
	4	0.3	0	0
JCo	Start	0.8	40	83
	End	0.6	36	
	2	0.6		
	4	0.6	39	105
VP	Start	0.3	0	0
	End	0.2	0	
	2	0	0	
	4	0		
GC	Start	0.2	0	0
	End	0.2	0	
	2	0	0	
	4	0		
LP	Start	0	0	0
	End	0.2		
	2	0.2	0	
	4	0	0	
RS	Start	0	0	0
	End	0.1		
	2	0	0	
	4	0	0	
Infusions of glucose				
SP	Start	1.0	26	
	½	1.0		
	2	1.1	26	
JCa	Start	1.5		
	½	1.5		
	2	1.5		
JS	Start	3.4		
	½	3.4		
	2	3.2		
TE	Start	1.2		
	½	1.2		
Regular meal				
AS	Start	0.5	0	
	1	0.6		
	3	0.4	0	
MP	Start	0.7	0	
	1	0.8		
	3	0.8	0	

may have resulted from the infusions, or may represent spontaneous fluctuations. On the other hand, in all the patients who had marked elevation of serum creatine initially, the creatine rose significantly after the casein hydrolysate, the peak occurring at the end of the infusion in all cases. The urinary excretion of creatine also rose and fell, usually lagging somewhat behind the changes in the serum. RF and JCo behaved differently from the others. In both, the concentrations of serum creatine, initially in the borderline range in which there may or may not be creatinuria, fell significantly after the infusions, in RF to the point where creatinuria ceased.

Initial and final creatine clearances were measured in 5 cases. In 3 instances (CP, JCo, and GM), they rose significantly, in 1 instance (DB) equivocally. The results, in general, confirm the observation of Tierney and Peters (4), that creatine clearances vary with the concentration of creatine in the serum.

Five duplicate analyses of the casein hydrolysate revealed no significant amounts of preformed creatine.

DISCUSSION

Of the subjects studied, 3 had no measurable amounts of creatine in their sera and 4 others (CV, EM, JSa, and FD) had traces only. This suggests that a zero value by this technique is not necessarily abnormal.

The lack of significant change in the serum creatine following a meal may be due to various factors. The carbohydrate may be without immediate effect, the amount of preformed creatine may be too small to affect the serum appreciably, the amino acids provided by the meal may not be utilized to an appreciable extent for synthesis of creatine. It is possible that creatine is formed, but is so rapidly distributed and utilized that its concentration in the serum does not rise. The acute disturbance of carbohydrate metabolism induced by intravenous injection of 25 grams of glucose evidently has no gross effect upon the general metabolism of creatine.

Since the casein hydrolysate contained no preformed creatine, the elevations of serum creatine after injections of this mixture signify that the formation of creatine increased. They cannot be attributed to failure of excretion because urine

creatine either increased or remained constant. Presumably the increments were derived from the 3 per cent of methionine and 5.5 per cent of arginine in the hydrolysates. Bloch and Schoenheimer (1) and Borsook and Dubnoff (6) have proved that these amino acids are the materials from which creatine is formed. It is possible that, in the 6 patients who did not develop hypercreatinemia and creatinuria, the synthesis of creatine was relatively inactive, that serum creatine rose in the others because of some particular demand for this compound or because the materials required for its synthesis were not diverted to other purposes.

It is more probable that the synthesis of creatine was equally active in all patients; but that its distribution, utilization, and disposal were retarded in those patients who had initially high serum creatine. The reactions to the amino acids in these experiments are quite comparable to the reactions to ingested creatine reported by Tierney and Peters (4). In the latter, synthesis can have played no part. The falls of serum creatine in JCo and RF may have denoted further acceleration of the processes by which creatine is removed from the blood. The low initial concentrations are merely evidences of the same phenomenon.

The experiments as a whole support the evidence of Tierney and Peters (4) that creatinuria denotes that serum creatine is greater than 0.5 mgm. per cent. In no case of this series was creatinuria encountered when serum creatine was below 0.5 mgm. per cent; in only one was it absent when serum creatine exceeded 0.8 mgm. per cent. The presence or absence of creatinuria in patients with serum concentrations between 0.5 and 0.8 mgm. per cent may be a mark of individual variability and technical errors, which may amount to 0.15 mgm. per cent.

SUMMARY

Creatinuria in persons suffering from a variety of diseases was found to be regularly associated with elevated serum creatine.

Serum creatine was not altered by the intravenous injection of 25 grams of glucose or by a large breakfast.

The serum creatine of subjects with initially high serum creatine rose and creatinuria appeared or increased after the intravenous injection of an enzymatic hydrolysate of casein.

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