Preliminary Communications

Pyruvate and Lactate Excretion in Diabetes Mellitus after Sodium Lactate

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Anderson and Marks (1962) showed that the reabsorption of pyruvate in the kidney tubules of normal subjects is nearly complete. In diabetics, while the plasma concentration of pyruvate may be twice that of normal subjects, the urinary excretion of pyruvate is usually three or four times greater (Takanami *et al.*, 1960; Anderson and Mazza, 1963; Anderson *et al.*, 1964). Thus the reabsorptive capacity for pyruvate in the diabetic may be reaching a maximum. In normal subjects almost complete reabsorption of lactate occurs. In diabetic patients, while the plasma lactate concentration may be nearly 50% higher, the urinary excretion is doubled or trebled. The renal clearance of lactate is thus increased in diabetics.

With cystinuria as an example, where there is a common defect in the reabsorption of the amino-acids cystine, lysine, arginine, and ornithine, an increased concentration in the blood of one amino-acid increases the excretion of the others, since they share a common reabsorptive mechanism. As it appeared that pyruvate and lactate might also share a common tubular reabsorptive mechanism, the renal lactate load was raised by giving 10 g. of neutral D-L-sodium lactate by mouth to try to increase the excretion of pyruvate in diabetic patients.

SUBJECTS AND METHODS

The test was conducted on 13 normal subjects and diabetic patients treated with insulin (Group 1), nine diabetics treated with chlorpropamide (group 2), and nine diabetics on diet alone (group 3). All those who were on either insulin or chlorpropamide had their usual medication before the lactate loading test was done, usually two hours after breakfast. At the start of the experiment two timed urine collections were made at 20-minute intervals, and a blood sample was taken between these collections. Directly after the second urine specimen was collected the patient drank 10 g. of neutral D-L-sodium lactate in solution. Twenty minutes after the

ingestion of the lactate a further blood sample was taken, and urine collections were made over the next two-hourly periods.

Blood and urinary pyruvate was measured by the enzymatic method of Marks (1961), and blood and urinary lactate by the method of Barker and Summerson (1941).

RESULTS

Table I shows the urinary pyruvate and lactate excretion of the four groups before and after ingestion of lactate. The Chart presents the urinary pyruvate excretion of the groups in

Mean urinary pyruvate excretion in normals and three diabetic groups before and after lactate ingestion.

TABLE I.—Urinary Pyruvate and Lactate Excretion Before and After the Administration of Sodium Lactate, Expressed as the Mean $\pm$ Standard Deviation; the Significance of the Results Obtained Compared with those of the Normal Subjects Under the Same Conditions is Shown

Group	Before Lactate		After Lactate			
	Pyruvate (μ g./min.)	Lactate (μ g./min.)	0-30 Minutes		30-60 Minutes	
			Pyruvate (μ g./min.)	Lactate (μ g./min.)	Pyruvate (μ g./min.)	Lactate (μ g./min.)
Normals	3.34 $\pm$ 1.49	36.3 $\pm$ 20.5	3.85 $\pm$ 1.95	106 $\pm$ 121.9	3.92 $\pm$ 2.72	333.4 $\pm$ 569.5
1	7.91 $\pm$ 5.94 (P < 0.001)	96.5 $\pm$ 76.8 (P < 0.001)	14.83 $\pm$ 11.60 (P < 0.001)	208.7 $\pm$ 140.5 (P < 0.2)	15.90 $\pm$ 16.74 (P < 0.02)	587.1 $\pm$ 629.0
2	6.72 $\pm$ 4.47 (P < 0.01)	81.8 $\pm$ 38.5 (P < 0.001)	9.05 $\pm$ 5.11 (P < 0.001)	190.6 $\pm$ 115.2 (P < 0.2)	9.01 $\pm$ 7.12 (P < 0.01)	556.2 $\pm$ 706.0
3	4.57 $\pm$ 2.35 (P < 0.05)	48.6 $\pm$ 29.0 (P < 0.2)	8.37 $\pm$ 7.16 (P < 0.05)	246 $\pm$ 144.3 (P < 0.1)	9.36 $\pm$ 6.33 (P < 0.01)	600 $\pm$ 516.4

TABLE II.—Blood Pyruvate and Lactate Before and 20 Minutes After the Administration of Sodium Lactate, Expressed as the Mean $\pm$ Standard Deviation; the Significance of the Results Obtained Compared with those of Normal Subjects Under the Same Conditions is Shown

Group	Before Lactate		After Lactate	
	Blood Pyruvate (μ g./100 ml.)	Blood Lactate (mg./100 ml.)	Blood Pyruvate (μ g./100 ml.)	Blood Lactate (mg./100 ml.)
Normals	413.1 $\pm$ 228.9	12.6 $\pm$ 5.3	470.0 $\pm$ 238.3	18.3 $\pm$ 6.2
1	632.7 $\pm$ 441.1 (P < 0.7)	16.9 $\pm$ 8.3 (P < 0.4)	986.1 $\pm$ 708.6 (P < 0.02)	20.5 $\pm$ 11.6 (P < 0.6)
2	466.9 $\pm$ 105.0 (P < 0.6)	12.9 $\pm$ 6.8 (P > 0.9)	544 $\pm$ 208.7 (P < 0.5)	15.8 $\pm$ 10.3 (P < 0.5)
3	487.1 $\pm$ 152.1 (P < 0.5)	8.5 $\pm$ 2.9 (P < 0.1)	609 $\pm$ 112.6 (P < 0.02)	15.3 $\pm$ 5.1 (P < 0.3)

graphical form. The statistical significance of the results in the three periods for diabetics was determined by comparing their value with that of the normal subjects for each period, the results being shown in Table I. The P factor was not evaluated for the lactate level in the 30–60-minute period after lactate ingestion, as there was too much scatter in the results.

Table II shows the blood pyruvate and lactate concentrations before and 20 minutes after ingestion of sodium lactate. After lactate by mouth there is a rise in blood pyruvate concentration in the diabetics, and the significance of the difference between their values and those of the normal subjects is apparent. A general rise in the blood lactate concentration showed that the lactate given by mouth was being absorbed.

DISCUSSION

The blood pyruvate concentration of the normal subjects before lactate ingestion was not significantly different from that of the three groups of diabetics. After lactate ingestion the blood pyruvate concentrations were increased in all groups. The increase in group 1 and group 3 diabetics was probably significantly greater than the increase in the normal subjects.

Before lactate ingestion the urinary pyruvate excretion of all the diabetic groups was greater than that for the normal subjects; in group 1 the difference was highly significant, in group 2 significant, and in group 3 probably significant. This finding is in agreement with previously reported work (Takanami *et al.*, 1960; Anderson and Marks, 1962). After lactate ingestion the urinary pyruvate excretion was increased in the normal subjects and in all the diabetic groups. The significance level of the differences between the groups 30 minutes after lactate ingestion was the same as before lactate ingestion. The increase in all the diabetic groups was considerably greater than in the normal subjects (see Chart).

It is evident that in all three of the diabetic groups there was some abnormality in their excretion of pyruvate, and that this abnormality was aggravated by the lactate load. The increase in the blood pyruvate concentration after lactate ingestion would not fully account for the increased urinary pyruvate excretion, assuming that the glomerular filtration rate did not alter appreciably during the test. The blood lactate concentrations before and after lactate ingestion were not significantly different in the normal subjects and the three diabetic groups. There was of course an increase in the blood lactate concentration in all the groups after ingestion of the sodium lactate, and this was reflected in the urinary excretion. There was a highly significant rise in lactate excretion in group 1 and group 2 diabetics compared with normals. This finding has been reported previously (Anderson and Mazza, 1963). There was no significant difference in the urinary lactate excretion of the normals and of the three diabetic groups after the lactate ingestion.

The marked increase in pyruvate excretions after lactate ingestion in all the diabetic groups as compared with normal subjects might well be due to the competition in the renal tubules between the very large amounts of lactate and pyruvate.

It is also possible that the lactate causes increased secretion of pyruvate from the tubules, or that the diabetic is able to convert more lactate to pyruvate. It must be remembered that the diabetic excretes high levels of lactate normally, and here the effect has been exaggerated. Certainly in this study lactate excretion seems to follow pyruvate, except in the case of the diabetics on diet alone, where the pre-lactate urinary lactate excretion was not significantly different from that of the normal subjects, though it was significantly different from the diabetics on chlorpropamide. The slightly lower blood lactate concentration is of interest. This may be a manifestation of the effect described by Krebs *et al.* (1965). They found that short-chain fatty acids and aceto-acetate, of which dieting diabetic patients would presumably have raised levels, accelerate gluconeogenesis from lactate.

These results have tended to support the suggestion of Moorhouse (1964) that diabetics have a metabolic defect in the handling of pyruvate. He found that all groups of diabetics had an abnormal blood pyruvate after an intravenous pyruvate load. The present work has shown that the diabetic kidney also reabsorbs pyruvate less efficiently than normal, and this is evident in all groups of diabetics under a lactate stress.

SUMMARY

The urinary pyruvate excretion following sodium lactate ingestion was studied in three groups of diabetics and a group of normal subjects. The abnormality in pyruvate excretion was more pronounced and detectable in the diabetic groups after lactate ingestion.

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