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Elevation of blood lactate and pyruvate levels in acute intermittent porphyria — A reflection of haem deficiency?

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Summary

Blood lactate concentrations after glucose loading were significantly higher in 6 patients with acute intermittent porphyria in clinical remission than in 6 control subjects and the percentage rise in glucose pyruvate and lactate concentrations were greater in the porphyric subjects than in the control group. It is postulated that the raised lactate levels in the porphyric patient group may reflect haem deficiency affecting the cytochromes of the terminal respiratory chain.

Introduction

The acute porphyrias are inherited diseases in which there is impaired haem biosynthesis [1]. Acute intermittent porphyria (AIP) is the commonest of these in the United Kingdom and is characterised biochemically by a reduced activity of the enzyme porphobilinogen (PBG) deaminase, which catalyses the third step of the haem biosynthetic pathway. As a result of this partial block in the haem pathway there is increased activity of the initial and rate controlling enzyme ALA synthase and overproduction of the porphyrin precursors ALA and PBG found prior to the enzyme defect. Affected individuals are at risk of developing acute attacks of neurovisceral dysfunction, the aetiology of which is unclear. One possible explanation for the neuropathy of AIP is haem deficiency in the nervous system [2].

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In patients suffering clinical attacks of AIP [3–5] increased pyruvate concentrations have been reported following a glucose load. The suggestion has been made that this reflects reduced activity of the electron transport chain [6]. An impairment in terminal oxidation would result in less availability of oxidised nicotinamide-adenine dinucleotide (NAD^+). This could arise through haem deficiency as the primary components of the respiratory chain comprise a series of haemoproteins. To elucidate further any association between AIP, haem deficiency and glycolysis, a study was carried out on pyruvate and lactate concentrations after glucose loading in patients with AIP in clinical remission.

Patients and methods

Six patients (5 female, 1 male) with AIP and 6 sex-matched control subjects were studied. The mean age of the porphyric patients was 32 years (range 23–38)

TABLE I

Glucose, pyruvate and lactate concentrations after glucose loading in six porphyric patients and six control subjects

Time (Min)	0	30	60	90	120
Glucose concentrations (mmol/l)					
Patients					
Median	4.7	7.4	7.6	6.0	7.1
Range	4.3–5.3	6.1–11.6	4.1–14.4	3.8–13.1	3.9–11.9
Controls					
Median	4.7	6.3	5.5	4.7	4.8
Range	4.5–5.1	4.9–8.6	3.9–9.9	3.7–8.2	3.6–6.2
Pyruvate concentrations (μmol/l)					
Patients					
Median	139	174	213	233	205
Range	83–293	114–323	131–274	120–265	119–217
Controls					
Median	169	157	190	209	197
Range	147–240	118–181	108–251	155–261	111–256
Lactate concentrations (mmol/l)					
Patients					
Median	1.3	1.4	2.0	2.1	1.9
Range	1.0–3.0	1.1–4.6	1.7–3.2	1.5–2.6	1.4–3.2
Controls			**	**	*
Median	1.2	1.2	1.2	1.3	1.4
Range	0.8–1.9	0.8–1.5	0.8–1.5	1.1–1.6	1.2–1.9

* Significantly higher than controls, $P < 0.05$.
** Significantly higher than controls, $P < 0.01$.

compared to a mean age of control subjects of 30 (range 22–44). In all six patients urinary excretion of porphyrin precursors was elevated, median 24 h urinary excretion of ALA being 155 μmol/24 h (range 98 to 260 μmol/24 h, normal < 40 μmol/24 h). All porphyric patients had suffered at least one attack of AIP requiring admission to hospital and diagnosis had been made on the basis of reduced activity of erythrocyte PBG deaminase and increased urinary excretion of porphyrins and precursors. All patients were in clinical remission at the time studied and none had a peripheral neuropathy. None of the patients or control subjects was thiamine deficient, all having normal erythrocyte transketolase activities prior to testing.

After an overnight fast, 50 g glucose was given at 0 and at 30 min. Blood was drawn for glucose, pyruvate and lactate at 30 min intervals from baseline to 120 min after the first glucose drink.

Urinary ALA, PBG and porphyrins and erythrocyte PBG deaminase as described previously [7] was measured. Blood glucose was measured by standard laboratory methods, blood lactate and pyruvate using the method of Hadjivassiliou and Reider [8]. Statistical comparisons between controls and porphyric patients were made using Wilcoxon Rank Sum tests, and Mann–Whitney *U* test.

Results

Blood glucose levels after glucose loading were not significantly different between control and porphyric patients (Table I). Pyruvate levels were similar in porphyric and control subjects but were at all times greater in porphyric subjects. Blood lactate levels were significantly higher in the porphyric patients (Fig. 1), being significantly raised at 60 min ($P < 0.01$), 90 min ($P < 0.01$) and 120 min ($P < 0.05$).

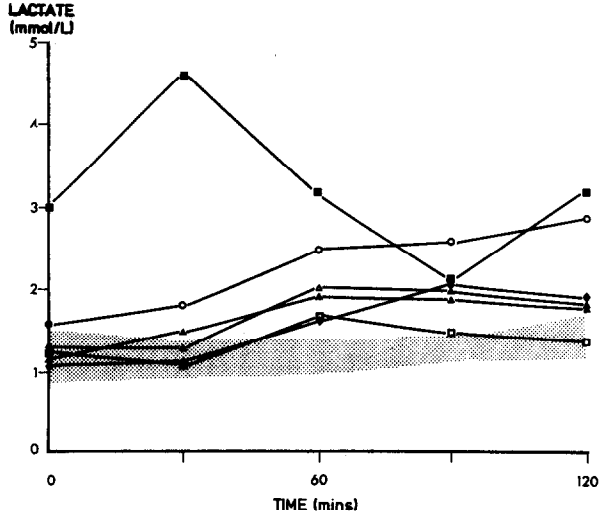

Fig. 1. Blood lactate levels after glucose loading in 6 porphyric patients. Shaded area represents mean ± SD in 6 control subjects.

TABLE II

Percentage change in glucose, pyruvate and lactate concentrations after glucose loading (calculated with respect to initial 0 time values)

Time (Min)	30	60	90	120
Glucose concentrations (mmol/l)				
Patients				
Mean	68.2 *	72.0	61.3	56.4 *
Range	38.6 to 141.7	−4.6 to 200	−13.6 to 178.7	−11.3–153.2
Control				
Mean	35.2	30.2	8.3	2.1
Range	0 to 68.6	−18.7 to 86.9	24.4 to 60.7	−26.5 to 22.2
% Change in pyruvate				
Patients				
Mean	29 *	44 *	53	36
Range	14 to 88	1 to 92	−18 to 110	−25 to −68
Controls				
Mean	−16	4	15	4
Range	−32 to 4	−38 to 8	−35 to 53	−35 to 48
Lactate concentrations				
Patients				
Mean	17.2 *	50.2 *	49.0	49.4
Range	−8.3 to 5.3	6.7 to 72.7	−30 to 110	6.7 to 90
Control				
Mean	1.6	10.6	20.8	32.4
Range	−25 to 50	−33.3 to 87.5	−36.8 to 100	−36.8 to 100

* $P < 0.05$ by Mann-Whitney U test.

When the differences were expressed as percentage change in each of these metabolites with respect to base-line values it was found that there were significantly greater rises in pyruvate, lactate and glucose levels in the patients with acute porphyria following the glucose load (Table II).

Discussion

Under anaerobic conditions, insufficient oxygen is available for the mitochondrial cytochrome system to maintain adequate NAD^+ levels for glycolysis and so this becomes dependent upon the conversion of pyruvate to lactate for generation of NAD^+. Hence, serum lactate levels often rise during exercise and an 'oxygen debt' is created. In this study, blood lactate levels after glucose were significantly higher in the porphyric than in the control subjects. Similarly, the glucose load caused a rise in pyruvate levels which were greater than the controls. This is consistent with a blockade at this level of intermediary metabolism. Both porphyric patients and control subjects were studied at rest and so anaerobic metabolism would not have occurred.

It has been postulated that the acute porphyrias are haem deficiency disorders and it is already well established that in AIP hepatic cytochrome *P*450 (monooxygenase) deficiency occurs, which leads to impaired drug metabolism and which can be corrected by exogenous haem [9]. That the neuropathy associated with AIP may be due to a reduction in vital haemoproteins required for oxidative metabolism in the nervous system has been suggested, but not proven [2].

Haem deficiency affecting the cytochromes of the terminal respiratory chain might be expected to lead to failure of production. Such an inhibition of the terminal electron transport system in AIP has already been proposed, based on experimental studies [10] and impairment of NADH oxidation has been reported in fibroblasts from patients with AIP [11]. A situation similar to that occurring under anaerobic conditions could therefore arise in acute porphyria with glycolysis becoming dependent upon the conversion of pyruvate to lactate. Our findings may, therefore, bring further support to the concept of AIP as a haem deficiency disease. There is one previous report of raised lactate levels in AIP [5]. The affected patients were in acute attack and both pyruvate and glucose tolerance were also abnormal, in distinction to this study where lactate levels rose in patients in clinical remission, independently of the blood glucose level. Should our patients develop further attacks of porphyria, then assays of blood lactate and pyruvate concentrations after glucose will be repeated, both before and after haem arginate administration. This will show if the rise in pyruvate and lactate is more marked during the porphyric crisis and if exogenous haem corrects the abnormally high levels.

Impaired glucose tolerance is well documented in AIP [5,12]. Most reports of abnormal glucose tolerance in acute porphyria refer to acute attacks when the impaired gastric emptying may be contributing. Interestingly, glucose tolerance has been found to return to normal after resolution of the acute attack [12].

While the clinical significance is unclear, the rise in pyruvate and lactate levels in patients with AIP may reflect an impairment of intermediary metabolism which exists when their disease is in clinical remission. Taken in conjunction with other metabolic defects associated with AIP, these results may contribute to the elucidation of the pathogenesis of this intriguing disease.

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