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In vivo and in vitro sodium pump activity in subjects with thyrotoxic periodic paralysis

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Abstract

***Objective*—To examine whether sodium pump activity plays a part in the pathogenesis of thyrotoxic periodic paralysis.**

***Design*—Measurement of platelet sodium-potassium ATPase and in vivo sodium pump activities in healthy subjects and thyrotoxic subjects with and without paralysis.**

***Setting*—University hospital in Hong Kong.**

***Subjects*—21 healthy subjects, 23 untreated thyrotoxic subjects, 13 untreated men with periodic paralysis, seven treated thyrotoxic subjects, and six treated men with periodic paralysis.**

***Main outcome measures*—Platelet Na^+, K^+-ATPase activity and plasma rubidium concentration after oral loading.**

***Results*—Median (range) platelet Na^+, K^+-ATPase activity in thyrotoxic subjects was 253 (169-821) μmol inorganic phosphate/h/g protein—significantly higher than that in healthy subjects (134 (81-180) μmol/h/g protein; $p<0.001$). Na^+, K^+-ATPase activity in those with periodic paralysis was 374 (195-1196) μmol/h/g protein, again significantly higher than that in healthy subjects ($p<0.001$) and that in other thyrotoxic subjects ($p<0.01$) despite similar degrees of hyperthyroidism. Activities in treated thyrotoxic subjects with and without periodic paralysis were 148 (110-234) and 131 (86-173) μmol/h/g protein respectively. Mean (95% confidence interval) plasma rubidium concentration five hours after oral administration in thyrotoxic subjects (7·0 (6·6 to 7·5) μmol/l) was significantly lower than in healthy subjects (10·2 (9·5 to 10·9) μmol/l; $p<0.001$) and higher than in those with periodic paralysis (6·0 (5·7 to 6·3) μmol/l; $p<0.01$).**

***Conclusions*—Sodium pump activity in untreated subjects with periodic paralysis is higher than in other thyrotoxic subjects, and this may be responsible for the hypokalaemia.**

Introduction

Hypokalaemic periodic paralysis, in association with thyrotoxicosis, occurs almost exclusively in oriental men[1-4] and has been reported to occur in 13-26% of thyrotoxic Chinese men.[2-4] It is about 70 times more

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common in men then women.[2] The paralysis usually follows ingestion of a carbohydrate meal, heavy exercise, or both.[4] The paralysis lasts for a short time and is occasionally associated with life threatening complications such as cardiac arrest[2] or respiratory failure.[5] Correction of hypokalaemia reverses the acute attack and subsequent treatment with β blockers or antithyroid drugs effectively prevents further attacks.[6]

Thyrotoxic periodic paralysis has been suggested to be genetically determined as its incidence is strikingly high among orientals[7] and it can be familial.[8] Furthermore, a higher prevalence of the haplotype A2, B22 in patients with periodic paralysis has been reported,[8] although this has not been confirmed by others.[9]

The pathogenesis of periodic paralysis is not fully understood. The associated hypokalaemia is believed to be due to a rapid influx of potassium into cells,[10 11] as in the familial type. An important factor in the transport of potassium into cells is the sodium pump sodium-potassium ATPase (Na^+, K^+-ATPase, EC 3.6.1.3). The sodium pump is known to be affected by thyroid status. The number and activity of sodium pumps in muscle[12] and white cells[5 13 14] are increased in patients with thyrotoxicosis. In experimental animals given triiodothyronine[15 16] or in cells cultured in vitro in the presence of triiodothyronine[17 18] Na^+, K^+-ATPase activity is stimulated. The increased entry of potassium into cells in patients with periodic paralysis may result from increased Na^+, K^+-ATPase activity. In this study we tested this hypothesis by measuring the platelet Na^+, K^+-ATPase activity in vitro together with in vivo assessment of sodium pump activity.

Subjects and methods

We studied five groups of subjects: healthy subjects who had no known illness and denied taking any drugs; thyrotoxic subjects who were not receiving treatment and who had raised plasma concentrations of free triiodothyronine and thyroxine and lowered thyroid stimulating hormone concentration at the time of the study; thyrotoxic subjects receiving treatment who had clinically and biochemically normal thyroid function; thyrotoxic subjects with periodic paralysis who were admitted to hospital with weakness or paralysis and studied within 48 hours of admission after correction of plasma potassium concentration and muscle weakness but before starting treatment with β blockers or antithyroid drugs, or both; and six subjects who had had episodes of periodic paralysis and who were receiving treatment and had clinically normal thyroid function at the time of study.

All studies were carried out with the full informed consent of those concerned and the study was approved by the ethics committee of the Chinese University of Hong Kong.

PLATELET NA^+, K^+-ATPASE ACTIVITY

The Na^+, K^+-ATPase activity in platelets was studied in all five groups of subjects: 15 healthy men, 15 untreated thyrotoxic men, seven treated thyrotoxic men, 12 untreated men with periodic paralysis, and six treated men with periodic paralysis. Blood samples were taken from all subjects in the morning, at least three hours after the last meal or after an overnight fast. The samples were taken into trisodium citrate (9 ml of blood to 1 ml of citrate) and heparinised tubes. Citrated blood was used for platelet studies, and plasma from heparinised blood was used for the measurement of electrolyte, creatinine, thyroid hormone, and thyroid stimulating hormone concentrations.

Platelet rich plasma was prepared as described by Turaihi *et al.*[19] The citrated blood was centrifuged at 160 *g* for 15 minutes at room temperature. Contamination of the plasma with erythrocytes and leucocytes was minimal, accounting for <0·5% of the platelet count. Na^+, K^+-ATPase activity was measured by a method based on the rate of release of phosphate by hydrolysis of ATP in the presence and absence of ouabain.[20] The platelet rich plasma was centrifuged and the platelet pellet was washed twice with magnesium chloride to remove any trapped plasma. The platelets were then lysed by freezing and thawing and then adding saponin solution (0·05% weight/volume). An aliquot of platelet lysate (0·1 ml) was added to each of six tubes and incubated with 0·1 ml of incubation medium containing (final concentration) sodium 100 mmol/l, potassium 15 mmol/l, ATP 5 mmol/l, magnesium 7 mmol/l, EDTA 1 mmol/l, TRIS-HCl buffer 50 mmol/l (pH 7·2 at 37°C). Ouabain at a final concentration of 1 mmol/l was added to two of these tubes. All tubes were incubated for 60 minutes at 37°C in a shaking water bath and the reaction was stopped by adding trichloroacetic acid (10% weight/volume). The tubes were then centrifuged and the phosphate content of the supernatant was determined by an automated method based on that described by Daly and Ertinghausen.[21] The precision of the assay, as determined by duplicate analysis, was 8·2% (n=14).

IN VIVO SODIUM PUMP ACTIVITY

In vivo sodium pump activity was measured in six healthy subjects (three men and three women aged 26-43 years), eight untreated thyrotoxic subjects (two men and six women aged 17-51 years), and seven untreated subjects with periodic paralysis (all men, aged 22-40 years).

In vivo sodium pump activity was assessed by measuring the changes in plasma rubidium concentration after an oral dose of rubidium chloride.[22] Rubidium chloride (8 mg/kg body weight) was dissolved in water mixed with orange squash and given in eight divided doses at 15 minute intervals. Venous blood samples were taken before and one and five hours after the last dose of rubidium chloride. The blood samples were centrifuged and the plasma was separated and stored at −20°C until analysis.

The plasma rubidium concentration was measured in a graphite furnace atomic absorption spectrophotometer (model AA-1475, Varian Techtron, Mulgrave, Australia) by the standard addition method.[23] Plasma samples were diluted with distilled water (one in 20), and the peak absorption was measured. In identical samples different amounts of aqueous standards of rubidium chloride were added and peak absorption was measured again. The peak absorption was plotted against the concentration of the added standard and the concentration of rubidium in the plasma was determined from the intercept on the x axis. The precision (coefficient of variation) of the method at a mean plasma rubidium concentration of 5·5 μmol/l was 5·3%. All samples in the study were analysed in one batch.

Plasma concentrations of thyroid stimulating hormone were measured by an immunochemiluminometric assay (Ciba Corning, United States) with a detection limit of 0·02 U/l. Plasma free triiodothyronine and thyroxine concentrations were determined by commercial immunoassay kits (Amerlex-M, Amersham, United States, for triiodothyronine, and Gammacoat two step assay, Baxter, Massachussetts, United States, for thyroxine). The analytical coefficient of variations of the methods were 6·4%, 4·8%, and 7·5% for thyroid stimulating hormone, triiodothyronine, and thyroxine respectively.

Differences between groups were compared by Student's *t* test for all parameters except platelet Na^+, K^+-ATPase activity, for which the Mann-Whitney U test was used. A p value less than 0·05 was considered significant.

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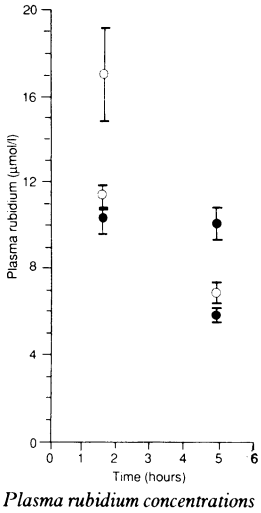
Results

PLATELET NA^+, K^+-ATPASE ACTIVITY

Table I shows the age and plasma concentrations of free triiodothyronine and thyroxine in the untreated patients with periodic paralysis. Table II summarises the results in the five groups of subjects studied. Plasma concentrations of triiodothyronine and thyroxine were raised and thyroid stimulating hormone concentrations were suppressed in all untreated thyrotoxic subjects with and without paralysis. Median (95% confidence interval) plasma concentrations of free triiodothyronine (19·6 (15·1 to 24·1) pmol/l) and free thyroxine (45·5 (38·4 to 52·6) pmol/l) in the untreated subjects with periodic paralysis were not significantly different from those of the thyrotoxic subjects without paralysis (table II). Platelet Na^+, K^+-ATPase activity in thyrotoxic subjects (median (range) 253 (169-821) μmol/h/g protein) was significantly higher ($p<0·001$) than that in healthy subjects (134 (81-180) μmol/h/g protein). In the 12 subjects with periodic paralysis the platelet Na^+, K^+-ATPase activity (374 (195-1196) μmol/h/g protein) was higher than that in healthy subjects ($p<0·001$) and that in other thyrotoxic subjects ($p<0·01$). In treated thyrotoxic subjects concentrations of free triiodothyronine and thyroxine and platelet Na^+, K^+-ATPase activity were lower than in untreated subjects. However, platelet Na^+, K^+-ATPase activity was still significantly higher than that found in healthy controls ($p<0·01$). In subjects with treated periodic paralysis the platelet Na^+, K^+-ATPase activity was not different from that of healthy subjects (table II).

IN VIVO SODIUM PUMP ACTIVITY

Plasma thyroid stimulating hormone and free triiodothyronine and thyroxine concentrations in the healthy subjects and thyrotoxic subjects with and without paralysis in whom in vivo sodium pump activity was measured were similar to those in tables I and II. The figure shows the plasma rubidium concentrations at one and five hours after the oral dose in the three groups of subjects. The mean (95% confidence interval) plasma rubidium concentration at five hours in thyrotoxic subjects (7·0 (6·6 to 7·5) μmol/l) was significantly lower than that in healthy subjects (10·2 (9·5 to 10·9) μmol/l, $p<0·001$). In subjects with periodic paralysis the five hour concentration (6·0 (5·7 to 6·3) μmol/l) was significantly lower than that in the thyrotoxic group ($p<0·01$). The plasma rubidium concentration at one hour also showed a similar picture (17·0 (14·9 to 19·2), 11·4 (10·9 to 11·9), 10·4 (9·7 to 11·2) μmol/l in healthy, thyrotoxic, and periodic paralysis groups, respectively).



Plasma rubidium concentrations in six healthy subjects (●), eight thyrotoxic subjects (○), and seven thyrotoxic subjects with periodic paralysis after oral administration of rubidium chloride (8 mg/kg body weight). Vertical bars represent 95% confidence intervals

TABLE I—*Details of subjects with thyrotoxic periodic paralysis*

Subject	Age (years)	In vivo sodium pump activity measured*	Free triiodothyronine (pmol/l)†	Free thyroxine (pmol/l)‡
1	26	Yes	20·6	—
2	49	Yes	16·1	44·0
3	22	Yes	16·4	—
4	31	Yes	11·0	37·7
5	20	Yes	12·4	42·5
6	39	Yes	26·7	—
7	40	No	18·1	56·4
8	38	No	9·0	26·0
9	22	No	31·2	55·3
10	39	No	22·9	54·4
11	32	No	34·5	55·3
12	39	No	16·4	36·7
13	26	No	21·5	—

All subjects had plasma thyroid stimulating hormone concentrations <0·02 mU/l.
*Platelet Na+, K+-ATPase activity was measured in all but subject 13.
†Reference range 3·3-8·2 pmol/l.
‡Reference range 7·0-21·5 pmol/l.

Discussion

Our results show that Na^+, K^+-ATPase activity in platelets is increased in thyrotoxic subjects with or without periodic paralysis. Increased numbers of sodium pumps, increased pump activity, and increased Na^+, K^+-ATPase activity have been shown in lymphocytes[5] and in a mixed leucocyte preparation[13] from thyrotoxic subjects. Increased ouabain binding capacity has also been shown in human skeletal muscle in hyperthyroidism.[12] The similarity between the changes in platelets and nucleated cells such as leucocytes and muscle cells in hyperthyroidism suggests that platelet Na^+, K^+-ATPase activity reflects that occurring in other tissues. The use of platelets is advantageous as the preparation is less tedious and requires a smaller volume of blood than is needed with leucocytes.

In a mixed leucocyte preparation Na^+, K^+-ATPase activity has been reported to be 22% higher in patients with hyperthyroidism.[13] In our study platelet Na^+, K^+-ATPase activity in hyperthyroid subjects was nearly double that of healthy subjects. Thus platelet Na^+, K^+-ATPase may be a useful tissue marker of thyroid status.

The ideal tissue in which to study periodic paralysis is skeletal muscle. However, muscle biopsy is invasive and platelets provide a readily accessible alternative. We found that the platelet Na^+, K^+-ATPase activity in untreated subjects with periodic paralysis was 80% higher than that in other untreated thyrotoxic subjects despite similar degrees of hyperthyroidism. In lymphocytes Oh *et al* were unable to show a significant increase in sodium pump mediated rubidium influx in patients with periodic paralysis, although they suggested that ouabain binding sites may be increased.[5] Other workers have studied erythrocytes to investigate periodic paralysis.[7 24] However, erythrocytes behave differently from other cells in thyroid disease[14 25-27] and are not a suitable cell type to study this condition.

To verify that platelet Na^+, K^+-ATPase activity measured in vitro reflects the sodium pump activity in vivo, we assessed the in vivo sodium pump activity. Rubidium is transported into cells by the sodium pump and the transport characteristics of rubidium and potassium are similar.[28] The disappearance of rubidium from extracellular fluid therefore depends largely on the sodium pump activity, and the plasma

TABLE II—*Plasma thyroid stimulating hormone and free triiodothyronine and thyroxine concentrations and platelet Na^+, K^+-ATPase activity in healthy men and thyrotoxic men with and without paralysis. Results are mean (95% confidence interval) except where indicated*

	Reference range	Healthy men (n=15)	Untreated thyrotoxic men (n=15)	Untreated men with periodic paralysis (n=12)	Treated thyrotoxic men (n=7)	Treated men with periodic paralysis (n=6)
Age (years)		35·1 (30·2 to 40·0)	41·4 (34·9 to 47·9)	33·1 (28·0 to 38·2)	41·0 (30·0 to 52·0)	34·8 (29·1 to 40·5)
Plasma thyroid stimulating hormone (mIU/l)	0·3–0·4	2·3 (2·1 to 2·5)	<0·02	<0·02	1·6 (0·8 to 2·4)	
Plasma free triiodothyronine (pmol/l)	3·3–8·2	4·5 (3·7 to 5·3)	20·2 (15·1 to 25·3)*	19·6 (15·1 to 24·1)*	6·7 (5·7 to 7·7)*	6·6 (6·4 to 6·8)*
Plasma free thyroxine (pmol/l)	7·0-21·5	11·5 (9·3 to 13·7)	38·1 (32·4 to 43·8)*	45·5 (38·4 to 52·6)*	14·0 (12·0 to 16·0)*	17·6 (16·4 to 18·8)*
Mean (range) platelet Na^+, K^+-ATPase activity (μmol/h/g protein)		134 (81 to 180)	253 (169 to 821)†	374 (195 to 1196)†‡	148 (110 to 234)†‡	131 (86 to 173)

*p<0·001 Compared with healthy subjects (Student's *t* test).
†p<0·001 Compared with healthy subjects (Mann-Whitney U test).
‡p<0·01 Compared with untreated thyrotoxic men (Mann-Whitney U test).

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concentration of rubidium is inversely related to the sodium pump activity. Skeletal muscle is the largest single tissue in the body. Thus it is likely that the plasma rubidium concentration mirrors skeletal muscle sodium pump activity. The lower plasma concentration of rubidium at one and five hours after an oral load in untreated thyrotoxic subjects shows that the sodium pump activity is increased, and this confirms results from in vitro studies in muscle and leucocytes.[12 13] In untreated subjects with periodic paralysis the plasma rubidium concentration was lower, and thus the activity of the sodium pump higher than in thyrotoxic subjects without paralysis. This supports our data from platelets. The observed differences in plasma rubidium concentration between groups could also be due to reduced absorption of rubidium or enhanced clearance by the kidney. However, renal clearance of rubidium is slow and the half life is between 20 and 50 days.[29] Thus it is unlikely that the observed differences are due to renal clearance. Rubidium is handled like potassium and it is unlikely that reduced absorption would have contributed to the observed changes. These results therefore indicate that higher Na^+, K^+-ATPase activity is a feature of thyrotoxic periodic paraalysis and that this enhanced activity may be responsible for the hypokalaemia seen in these patients.

In treated subjects with periodic paralysis the platelet Na^+, K^+-ATPase activity was similar to that found in healthy subjects, showing that the sodium pump activity returns to normal with treatment. Thus the higher platelet Na^+, K^+-ATPase activity seen in subjects with periodic paralysis is likely to be due to increased sensitivity to thyroid hormones and is demonstrable only in the presence of hyperthyroidism.

We conclude that platelet Na^+, K^+-ATPase activity and in vivo sodium pump activity are increased in thyrotoxicosis. These findings agree with those in other tissues in vitro, although the size of the change is greater in platelets than has been reported in leucocytes. In subjects with periodic paralysis both platelet activity and in vivo sodium pump activity are increased to a greater degree than those in other thyrotoxic subjects despite similar increases in thyroid hormone concentrations. The difference between the two groups disappears when a euthyroid state is restored with treatment.

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ONE HUNDRED YEARS AGO

The announcement of the investment of Lady Roberts and certain of the army hospital nurses with the Order of the Red Cross, testifies once more to the strong interest felt by Her Majesty in the welfare of her invalid soldiers and the care of the sick. It were much to be wished that the same lively interest and spontaneous regard for hospital administration were shown by the War Office. At the present moment, if we had to point to a conspicuous example of a highly defective hospital placed under conditions in which it is impossible that the interests of the sick can be properly regarded, we should, we regret to say, have to point to the hospital establishment for the treatment of the soldiers at Aldershot suffering from infectious and contagious diseases. While large sums are being expended on all sides in barracks and mess-rooms, the hospital, which has to provide for this important class of diseases in a camp of some thirteen thousand men, their wives, and children, is so neglected as to its buildings that it is not possible to provide adequate safeguards for the spread of infection from one class of patients to the other. This neglect of an obvious duty to the sick is emphasised by the fine buildings which are arising on the same lines for other purposes, which might have been postponed. The necessity for ameliorating the insanitary and defective structural arrangements now existing, is, we believe, very fully admitted; but for some unknown reason it appears to be indefinitely postponed. Meantime, the mess-rooms flourish while the hospitals suffer.

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