POTASSIUM AND MUSCULAR DISORDERS

BY

J. N. CUMINGS *

From the Biochemical Laboratory, The National Hospital, Queen Square, London

(RECEIVED 18TH NOVEMBER, 1941)

It has been shown in a previous paper (Cumings, 1939*b*) that the potassium content of muscle was abnormal in two diseases, except for conditions in which fat or fibrous tissue replacement of muscle occurs. Some further muscles from a variety of diseases have since been examined and the results have not given rise to any change of opinion. It has also been shown (Cumings, 1939*b*, 1940) that muscles from myasthenia gravis contain an excess of potassium, which was liberated after prostigmin injection, with a resulting increase of the serum potassium level. There was, however, no increased urinary excretion of potassium, the potassium returning to the muscles as the muscles became weaker.

The amount of potassium present in excess in the serum did not account for all the potassium which was estimated to have been liberated from the muscles. Two more patients with myasthenia have been investigated to confirm the previous results and to determine whether the red cells also showed an increase in their potassium content, and the results are recorded. Some experimental results are also recorded in which rabbits were injected with substances extracted from gelsemium roots in an endeavour to produce muscular disorders in any way comparable to myasthenia.

Potassium Content of Muscles in Various Conditions

The potassium content of muscles taken at biopsy from a variety of diseases was estimated as previously described (Cumings, 1939*a*), and the results are seen in Table 1, together with the effect prostigmin (mgm. i) had upon the potassium content of the muscle in some of the disorders.

It is seen that in the majority of diseases there is no abnormality in potassium content. The potassium contents found in muscles with fat replacement, such as in the patient with myopathy, and in muscle in the case of myotonia are in accord with previous findings. The patient with familial periodic paralysis showed a normal potassium content during the non-paralytic stage. It was, unfortunately, not possible to obtain muscle during an attack of weakness.

* A grant was received from the research funds of the National Hospital towards part of the expenses.

TABLE 1.—POTASSIUM IN MUSCLES IN DISEASE

NAME	DISEASE	POTASSIUM IN GRAMMES PER CENT. OF DRY WEIGHT	
		BEFORE PROSTIGMIN	AFTER PROSTIGMIN
F. S. ..	Myopathy with marked fibrosis	0.23 0.19	—
T. ..	Tetanus	1.18	—
C. ..	Hyperthyroid	1.44	1.12
B. ..	Myxœdema	0.63	1.4
C. ..	Myotonia	0.54	—
W. ..	Late myopathy	1.26	—
K. ..	Familial periodic paralysis—non-paralytic stage	0.82	—
R. ..	Parathyroid tumour— Before operation After operation	0.40 1.3	0.193 1.6

The patient with a parathyroid tumour gave a very interesting result and is the only example of variation from the previous findings. The patient came to hospital complaining of muscular weakness, but she was found to have a parathyroid tumour, which was successfully removed. Subsequently her weakness slowly disappeared. Muscle taken prior to operation showed a low potassium, with a diminution of potassium after prostigmin, but when the patient was well, both resting muscle and muscle after prostigmin showed normal potassium levels. It would appear that the muscular weakness was associated with a low potassium level in the muscles. The phosphate level was raised to 1.94 per cent. by dry weight. It is not possible on this single example to offer any explanation, and it is the one variation found in this series from those previously recorded.

Myasthenia and Potassium

Two patients with severe myasthenia were examined in a manner previously described (Cumings, 1940), with, however, a few variations. The diet—a war-time one—was somewhat more liberal in its content of potassium and was well tolerated, except that one patient vomited once, necessitating an estimation of potassium in the vomit. The patients as a result were in positive potassium balance. The potassium content of the whole blood as well as that of the serum was estimated. Potassium was added to the diet for the latter part of the experiment in the same dosage and in the same manner as previously, and prostigmin injections (mgm. i) were given on two occasions to each patient. The time relationship of these procedures can be seen from Figs. 1 and 2 on which the urinary excretions of potassium are recorded.

Results

The effect of the prostigmin injections on the serum and whole blood potassiums are given in Table 2.

R

TABLE 2.—POTASSIUM AND INORGANIC PHOSPHATE IN BLOOD BEFORE AND AFTER PROSTIGMIN

	MR. S.				MRS. T.			
	SERUM		WHOLE BLOOD		SERUM		WHOLE BLOOD	
	POTAS- SIUM	INOR- GANIC PHOS- PHATE	POTAS- SIUM	INOR- GANIC PHOS- PHATE	POTAS- SIUM	INOR- GANIC PHOS- PHATE	POTAS- SIUM	INOR- GANIC PHOS- PHATE
Before first prostigmin injection	17.6	3.5	104.6	18.4	16.9	2.1	112.6	10.0
$\frac{3}{4}$ hour after first prostigmin injection	20.2	3.5	110.0	17.6	18.1	2.5	145.0	14.0
Before second prostigmin injection	26.0	4.0	164.4	27.2	28.6	3.8	175.5	16.4
$\frac{3}{4}$ hour after second prostigmin injection	30.1	4.1	209.4	19.2	34.2	3.4	192.5	16.4

All results in milligrams per cent.

Serum sodium figures showed no variation between each pair of results.

The effect of prostigmin was similar clinically and biochemically to that found before, and in addition there is an increase of potassium in the red cells. The increase of potassium in the serum is not quite so marked as was seen previously, and may have been due to two factors. One reason was that both patients were in a positive potassium balance, and the other because neither of these patients was so severely affected with the disease as were the two previous patients.

The daily intake of potassium is recorded in Table 3. The first of the two patients received exactly the same foods and the same quantity of them each day, and it was this patient who vomited once.

TABLE 3.—INTAKE OF POTASSIUM

DAY OF EXPERIMENT	MR. S.		MRS. T.	
	DIET	MEDICINE	DIET	MEDICINE
1	1.254 gm. of K.		1.426 gm. of K.	
2	1.254 "		1.368 "	
3	1.254 "	3 gm. of K.	1.691 "	
4	1.254 "	3 "	1.286 "	3 gm. of K.
5	1.254 "	3 "	1.947 "	3 "
6	1.254 "	3 "	1.526 "	3 "
7	1.254 "	3 "	1.567 "	3 "
8	1.254 "	3 "	1.254 "	3 "
9			1.332 "	3 "
10			1.059 "	3 "
TOTAL . .	10.032 gm. of K.	18.0 gm. of K.	14.456 gm. of K.	21.0 gm. of K.

The potassium balance of both patients is given in Table 4, which shows the total intake and total excretion of potassium.

TABLE 4.—POTASSIUM BALANCE

	MR. S.	MRS. T.
K intake in food	10.032 gm.	14.456 gm.
K intake in medicine	18.0 ..	21.0 ..
Total K intake	28.032 ..	35.456 ..
K output in urine	15.023 ..	27.347 ..
K output in faeces	3.060 ..	1.736 ..
K output in vomit	0.079 ..	
Total K output	18.162 ..	29.083 ..
BALANCE	+9.87 gm. for 8 days. +1.23 gm. per day.	+6.373 gm. for 10 days. +0.637 gm. per day.

Whereas both patients previously examined were in negative balance, these two were definitely in positive balance.

The urinary excretion is set out in Figs. 1 and 2, together with the times of the prostigmin injections, and the days on which additional potassium was administered.

Fig. 1.

CASE MST URINARY EXCRETION OF POTASSIUM

Fig. 2.

It is seen that there was no increased urinary excretion of potassium as a result of the prostigmin, and that this is in accord with the previous experiments. Faecal excretion is given in Table 5 and shows no increase of potassium following prostigmin.

TABLE 5.—EXCRETION OF POTASSIUM IN STOOLS

DAY OF EXPERIMENT	MR. S.		MRS. T.	
	WEIGHT OF STOOLS, DRIED	TOTAL AMOUNT OF K PRESENT	WEIGHT OF STOOLS, DRIED	TOTAL AMOUNT OF K PRESENT
	GRAMMES	GRAMMES	GRAMMES	GRAMMES
1	—	—	—	—
2	32.0	1.216	7.8	0.110
3	—	—	14.9	0.249
4	5.9	0.173	16.65	0.082
5	5.7	0.62	2.7	0.010
6	—	—	26.35	0.208
7	—	—	12.6	0.32
8	—	—	16.2	0.078
9	16.8	0.706	—	—
10	12.5	0.345	12.5	0.192
11	—	—	17.5	0.478

Discussion

It is seen that the results obtained in these investigations on the two patients on a positive potassium balance, although conducted under some difficulties, owing in part to food rationing, were in agreement with those of previous experiments. It is also seen that the red blood cells show some increase of potassium content after prostigmin injections, and that the increase in whole blood potassium more nearly approximates to the amount of potassium liberated from affected muscles, whereas in the previous experiments the increased amount found in the serum was not sufficient to account for the total amount of potassium that one would expect to have been set free from the affected muscles. However, one would not expect to find a large amount of potassium being taken up by the red cells, as it has been shown by Hahn, Hevesy, and Rebbe (1939) in their experiments conducted with ^{42}K —a radioactive isotope of potassium—that the red cells only took up a relatively small amount of potassium, whereas muscle was able to take up nearly three times this amount of ^{42}K . Davson and Danielli (1938) showed that normal red cells prior to hæmolysis liberated little potassium, so that one would expect that the bulk of the potassium liberated from the muscles would be found in the plasma if it is to be returned again to the muscles. It is seen that there is no increase of urinary potassium after the prostigmin injections, and this is in accord with the previous results.

It had been suggested that a lack of nerve impulses to the muscles might result in an increase of muscle potassium. It was possible to show that this is not so both in human muscle and also experimentally in animals. One patient who had a spinal anæsthetic for a lower limb amputation had four samples of muscle removed after thirty minutes complete paralysis. None of the muscles showed a raised potassium content. Another patient who had a completely paralysed muscle after a severance of the motor nerve had a biopsy two months after the injury, and the muscle contained a normal amount of potassium. These results are recorded in Table 6, together with the results obtained from the animal experiments. Rabbits under nembutal anæsthesia were used for these experiments and samples of muscle were taken at varying intervals up to $2\frac{3}{4}$ hours after the nerve supplying the muscle had been cut. Another rabbit had a tourniquet applied to the hind leg, completely obstructing the arterial supply, but the potassium content was very similar before and $1\frac{1}{2}$ hours after this procedure.

The results obtained in these and preceding experiments all suggest an error in the potassium content of muscle primarily associated with myasthenia but not necessarily causing it. It is of interest here to note that Needham *et al.* (1941) have recently conducted some very interesting and instructive experiments. They have approached the subject of muscular activity and its relationship to potassium from a different aspect, using myosin birefringence and the action potassium and adenylypyrophosphate has upon it. They state that from previous work it would appear that adenylypyrophosphatase is either myosin or a related protein, and that muscular contraction is essentially a

molecular contractility of protein chains. Their own experiments indicate that adenylypyrophosphate has a direct influence on the shape of the myosin particles. Further, they found that a certain amount of potassium in contact with myosin caused a decrease of flow birefringence, i.e. a decrease in asymetry of the molecule and so a shortening of the particles and possibly a diminution in size also. However, when the amount of potassium was further increased the flow birefringence returned somewhat. There would thus appear to be a definite relationship between the amount of potassium present and the particle size of the myosin, but these results only relate to in vitro experiments, and may not be absolutely comparable to the conditions occurring in the actual muscle fibrils. v. Muralt (1932) has also shown that during a single isometric twitch the birefringence decreases and returns to normal by the end of relaxation. Whether this is associated with a variation in muscle potassium at the same time is not known. Fenn and Cobb (1936) in animals obtained a loss of potassium from muscles during exercise, and Keys (1940) showed an increase in plasma potassium after short exercise, although in these experiments the red cell potassium decreased. Cumings and Maas (1939) found no such alterations in serum potassium in normal human subjects, although in myotonia there was a decrease of serum potassium following exercise. It is possible that it is the relationship the muscle potassium bears to the potassium in the surrounding fluid that is the important factor, and if this is so it might explain the beneficial clinical results Laurent and Walther (1935) obtained in myasthenia with large doses of potassium by mouth, with subsequent increase of serum potassium. It does seem possible that the work of Needham as applied to myasthenia might yield valuable results. However, there is no evidence to show whether there is an error in the nature of the myosin or of the metabolism of potassium and its relationship to myosin, or whether some other factors controlling potassium metabolism are concerned.

TABLE 6.—EFFECT OF NERVE SECTION ON POTASSIUM CONTENT OF MUSCLE

Case 1	Four samples of muscle removed 30 minutes after spinal anæsthetic.						
	K gm. per cent. by wet weight ..	0.2	0.27	0.26	0.31		
	K gm. per cent. by dry weight ..	0.7	0.92	0.9	1.05		
Case 2	Muscle 2 months after complete nerve section.						
	K gm. per cent. by wet weight ..	0.31					
	K gm. per cent. by dry weight ..	0.93					
Rabbit 1 2 2 (opposite side)	Time, after nerve section						
	K gm. per cent. dry weight	Before nerve section	½ min.	5 mins.	30 mins.	60 mins.	90 mins.
		0.9	1.0		0.8		0.7
		1.5		1.5		1.7	
		1.5					1.4
							1.7 after complete arterial obstruction.

Marenzi (1938), from his experiments with cortico-suprarenal hormone, suggested that this substance regulates the fixation of potassium in the liver and the heart, but not in muscle, and also that it controls the renal excretion of potassium, as he found that although there was an increase of serum potassium after administration of this substance following suprarenal removal in animals, there was no increase of urinary excretion of potassium. Ferrebee *et al.* (1941) found that the administration of desoxycorticosterone acetate to dogs produced muscular weakness, with a loss of muscle potassium, but that there was also an increased urinary excretion of potassium.

Experiments with Gelsemium

It was thought possible to find a drug that would produce muscular weakness in animals and that this would perhaps enable one to investigate the relationship of potassium to muscular activity more easily. Gelsemium was chosen as being likely to give rise to such conditions, as Chou, in a series of papers (1931*a, b, c*) had succeeded in producing in rabbits some degree of muscular weakness. Chou had used both the American yellow jasmine and later a Chinese variety, Kou-Wen (*Gelsemium Elegans* Bth.). Both these plants were obtained, and the technique used by Chou followed as closely as his descriptions allowed, using the rhizome and roots ground to a powder before extracting with alcohol and with acid. Rabbits were then tested with varying doses of all extracts obtained, but in no case was there any muscular weakness, nor did the rabbits appear in any way affected. The serum potassium was estimated before and after the intravenous injections and no change took place, e.g. one rabbit had serum potassiums of 27.8 mgm. per cent. before and 24.9 mgm. per cent. three hours after the injection. One rabbit was given Kou-Wen to eat in 100 gm. doses a day, and although it has been said that parts of the plants are fatal to man if eaten, this animal showed no abnormalities. It has not therefore been possible to produce muscular weakness in animals using gelsemium root.

Summary

The potassium content of muscle in a variety of diseases has been estimated.

Potassium balance experiments on two patients with myasthenia gravis were conducted. Red blood cells as well as serum showed an increased potassium content after prostigmin injections, but no increased urinary excretion took place. These results are discussed in the light of recent physico-chemical work.

Division of the motor nerves to muscles does not affect their potassium content.

Substances extracted from the roots of American and Chinese varieties of the yellow jasmine produced no muscular disorders in rabbits.

My thanks are due to Dr. Grainger Stewart and Dr. J. Purdon Martin for allowing me access to their patients, to Mr. Harvey Jackson, F.R.C.S., and Mr. A. J. Cokkinis, F.R.C.S., for their help; and to Messrs. British Drug Houses for so kindly obtaining for me supplies of the gelsemium roots.

REFERENCES

- Chou, T. Q. (1931a). *Chin. J. Physiol.*, **5**, 131.
 — (1931b). *Ibid.*, 295.
 — (1931c). *Ibid.*, 345.
 Cumings, J. N. (1939a). *Biochem. J.*, **33**, 642.
 — (1939b). *Brain*, **62**, 153.
 — (1940). *J. Neurol. Psychiat.*, **3**, 115.
 Cumings, J. N., and Maas, O. (1939). *Brain*, **62**, 422.
 Davson, H., and Danielli, J. F. (1938). *Biochem. J.*, **32**, 991.
 Fenn, W. O., and Cobb, D. M. (1936). *Amer. J. Physiol.*, **115**, 345.
 Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity, M. K., Atchley, D. W., and Loeb, R. F. (1941). *J. clin. Invest.*, **20**, 445.
 Hahn, L., Hevesy, G., and Rebbe, O. (1939). *Nature, Lond.*, **143**, 1,021.
 Keys, A. (1940). *Proc. Soc. exp. Biol. N.Y.*, **43**, 395.
 Laurent, L. P. E., and Walther, W. W. (1935). *Lancet*, **1**, 1,434.
 Marenzi, A. D. (1938). *Endocrinology*, **23**, 330.
 v. Muralt, A. (1932). *Pflüg. Arch. ges. Physiol.*, **230**, 299.
 Needham, J., Shih-Chang Shen, Needham, D. M., and Lawrence, A. S. C. (1941). *Nature, Lond.*, **147**, 766.