THE RÔLE OF POTASSIUM IN MYASTHENIA GRAVIS

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(RECEIVED 28TH NOVEMBER, 1939)

It has been shown that the affected muscles of patients suffering from myasthenia gravis contain more potassium than normal muscles (Cumings, 1939*b*), and that after the subcutaneous administration of prostigmin to myasthenic patients, the concentration of potassium in their muscles fell to a normal level, and also in one of the cases recorded in that paper the serum potassium was observed to rise as the muscle potassium fell. The present paper deals with a study of the fate of the potassium leaving the muscles.

Two patients with severe myasthenia affecting the muscles of the extremities as well as those of the neck were chosen, and for the period of the experiment were given a diet containing a known amount of potassium. The meals were prepared from weighed quantities of milk, sugar, apple, tomato, bread, butter, chicken, fish, egg, potato, cheese, and rice, and the amount of potassium was determined in each of these foods. Distilled water was used for all purposes. Although one of the two patients received a rather more liberal diet and one which at the same time contained a larger amount of potassium, neither patient received quite as much potassium in their food as a normal person would have done.

The urine was collected in three 4-hourly periods during the day, and one 12-hour period during the night (e.g. from 8 a.m. to 12 noon, 12 to 4 p.m., 4 to 8 p.m., and 8 p.m. to 8 a.m.). The stools were collected separately, charcoal being used to demarcate the periods. The volumes of each urine specimen, and the weights of the dried stools were recorded.

Neither patient received prostigmin or any other therapy for the first two experimental days, but on the third each was given prostigmin (mgm. 1) subcutaneously at the end of one of the 4-hourly periods (at 4 p.m.). Each day from the fourth day to the end of the experimental period both patients were given 3 gms. of potassium in the form of dipotassium hydrogen phosphate. The measure was washed out with distilled water after each dose and the washings administered to the patients.

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

TABLE 1.—SERUM POTASSIUM BEFORE AND AFTER PROSTIGMIN

	MISS M. (MYASTHENIA)	MRS. C. (MYASTHENIA)	A.B. (NORMAL)	K.S. (NORMAL)	R.N. (NORMAL)
	17.5 mgm. % of K	16.9 mgm. % of K	15.0 mgm. % of K	22.4 mgm. % of K	19.0 mgm. % of K
Before first prostigmin injection	23.3 "	30.0 "	15.2 "	20.7 "	18.3 "
45 mins. after first prostigmin injection	29.2 "	34.7 "			
Before second prostigmin injection	39.1 "	42.5 "			
45 mins. after second prostigmin injection					

Further subcutaneous injections of prostigmin (mgm. 1) were given at 4 p.m. on the sixth day to one patient, and on the seventh day to the other patient, blood being taken before and 45 minutes after the injections. The experimental periods ended 40 hours after these last injections of prostigmin.

The potassium in the blood sera, urines, fæces, and foods was determined by the method previously used (Cumings, 1939a). The inorganic phosphate in the urine and fæces were estimated by Fiske and Subbarow's method (1925).

Results

Effect of Prostigmin on the Serum Potassium.—Table 1 shows the amounts of potassium found in the serum before and after the injection of prostigmin in the two patients and also in three normal subjects after one dose of prostigmin. The figures show that no alteration in serum potassium took place in the normal persons, but in both patients the administration of prostigmin was followed by an increase in the serum potassium, and that adding very large amounts of potassium to the diet raised the resting level of the serum potassium, but did not prevent the increase of that level after prostigmin. Clinically the effect of the prostigmin injection was excellent. The general muscular improvement was particularly rapid in the case of Miss M., who experienced considerable difficulty in swallowing.

Intake of Potassium.—Before considering the excretion of potassium, the daily intake of that substance is shown in Table 2. It is seen that apart from the first day there was a fairly constant amount of potassium in the food. It would seem unlikely therefore that the small variation in the potassium intake could account for the alterations in the level of serum potassium which followed the injection of prostigmin.

TABLE 2.—INTAKE OF POTASSIUM

DAY OF EXPERIMENT	MISS M.		MRS. C.	
	DIET	MEDICINE	DIET	MEDICINE
1	0.528 gm. of K.	—	0.539 gm. of K.	—
2	0.853 "	—	0.623 "	—
3	0.983 "	—	0.728 "	—
4	0.816 "	3.0 gm. of K.	0.784 "	3.0 gm. of K.
5	0.745 "	3.0 "	0.780 "	3.0 "
6	0.824 "	3.0 "	0.662 "	3.0 "
7	0.732 "	3.0 "	0.714 "	3.0 "
8	—	—	0.745 "	3.0 "
Total	5.481 "	12.0 "	5.575 "	15.0 "

Excretion of Potassium.—The excretion of potassium in the urine from the two patients is shown in Figs. 1 and 2. It will be seen that there was no increased excretion of potassium after the administration of prostigmin. A considerable increase did take place when the potassium was added to the diet. This increase, moreover, took place within 4 hours, so that any increase in the

CASE MISS M. URINARY EXCRETION OF POTASSIUM.

Fig. 1.

CASE. MRS C. URINARY EXCRETION OF POTASSIUM

Fig. 2.

urinary excretion of potassium consequent on the rise of serum potassium after prostigmin should have been seen within this same period.

The excretion of potassium in the stools is shown in Table 3. It is seen that no increased excretion of potassium has taken place at any time except on the fifth day of the experimental period in the case of Miss M. This is probably due to the slightly larger quantity of stool and because the patient was somewhat constipated for the first few days.

TABLE 3.—EXCRETION OF POTASSIUM IN STOOLS

DAY OF EXPERIMENT	MISS M.		MRS. C.	
	WEIGHT OF STOOLS (DRIED)	TOTAL AMOUNT OF K PRESENT	WEIGHT OF STOOLS (DRIED)	TOTAL AMOUNT OF K PRESENT
	GM.	GM.	GM.	GM.
1	—	—	—	—
2	—	—	47.5	0.751
3	—	—	—	—
4	13.5	0.309	39.2	0.786
5	27.0	1.118	—	—
6	14.5	0.423	—	—
7	}	0.636	}	0.870
8		0.895		—
9		—		0.711

Excretion of Inorganic Phosphate.—The figures for the excretion of inorganic phosphate in the urine and faeces from the two patients are given at the end of the paper, and it can be seen that no significant alterations have taken place as the result of the prostigmin injections.

Table 4 shows the potassium balances of the two patients over the whole period of the experiment.

TABLE 4.—POTASSIUM BALANCE

	MISS M.	MRS. C.
K intake in food	5.481 gm.	5.575 gm.
K intake in medicine	12.0 gm.	15.0 gm.
Total K intake	17.481 gm. for 7 days	20.575 gm. for 8 days
K output in urine	14.975 gm.	20.217 gm.
K output in faeces	3.381 gm.	3.118 gm.
Total K output	18.356 gm. for 7 days	23.335 gm. for 8 days
Balance	—0.875 gm. for 7 days —0.125 gm. per day	—2.760 gm. for 8 days —0.345 gm. per day

Discussion

One of the actions of prostigmin in myasthenia gravis is to liberate potassium from the affected muscles into the circulating blood. The total amount of this liberated potassium, which is in the blood, may be as much as 0.5 gm. (as calculated from the figures given in Table 1). It seemed possible that some of

this amount might have been found in the urine within a few hours after the administration of prostigmin. The urinary excretion of potassium, however, did not increase after prostigmin. Although the potassium in the diet varied somewhat from day to day, this variation did not cause any fluctuation of potassium excretion such that the sudden excretion of 0.5 gm. of potassium would not have been easily apparent. (Figs. 1 and 2, and Table 3.)

TABLE 5.—ACTION OF PROSTIGMIN UPON THE POTASSIUM CONTENT OF MUSCLE

TIME RELATIONSHIP	CLINICAL CON- DITION AT THE TIME MUSCLE WAS REMOVED	K IN GM. PER CENT. OF DRY WEIGHT OF MUSCLE	K IN GM. PER CENT. OF WET WEIGHT OF MUSCLE	PHOSPHATE AS P IN GM. PER CENT. OF DRY WEIGHT OF MUSCLE	SERUM K MGM. PER CENT.
1.30 Prostigmin given. 3.30 Muscle and blood removed.	Normal except for very slight weakness of eye muscles.	1.23	0.32	0.92	27.4
5.15 Muscle and blood removed.	Marked weak- ness in many muscles.	1.89	0.44	1.12	20.4
5.20 Prostigmin given. 5.50 Muscle and blood removed.	No weakness	1.14	0.265	1.03	31.9

It would seem that the potassium liberated from the muscles into the blood must have remained for a time in the blood and then to have returned to the muscles. This seems the more probable since the potassium in the muscles rises again when the action of prostigmin wears off (*vide infra*). A patient, Mr. J., with severe myasthenia gravis was receiving four and sometimes five doses of prostigmin daily, and although each dose produced a rapid clinical improvement this improvement persisted for only about 4 hours. A biopsy was performed 2 hours after a dose of prostigmin; $3\frac{1}{2}$ hours after this injection the patient became very weak and another sample of muscle was removed, after which prostigmin (mgm. 1) was again given. A third sample of muscle was taken $\frac{1}{2}$ hour later. Blood was taken each time muscle was removed. The potassium found in the three specimens of sera and in the three samples of muscle were estimated, and the results are seen in Table 5 together with the values for the phosphate found in the muscles. It is seen that the levels of potassium found in the second and third samples of muscle are in agreement with those recorded in my previous paper, and, moreover, that there was a slight increase in the amount of potassium found in the muscle 2 hours after prostigmin, as compared with the amount found after $\frac{1}{2}$ hour. It is also seen that the amount of potassium in the muscle increased considerably between 2 and $3\frac{1}{2}$ hours after prostigmin, during which time the clinical condition of the patient deteriorated. It therefore appears that the degree of muscular weakness is associated with the amount of potassium present in the muscle.

The fall in muscle potassium after the administration of prostigmin was accompanied by a small fall in the phosphate content.

The serum potassium was normal prior to prostigmin, it rose $\frac{1}{2}$ hour after the injection, and had already begun to fall 2 hours later, at a time when the muscle potassium had begun to increase. This supports the view postulated above that some at least of the potassium liberated from the muscles after prostigmin is retained in the blood serum and not excreted in the urine, and that it returns to the muscles as the action of prostigmin wears off and the symptoms of myasthenia return.

Further work is now in progress to determine the factors controlling this return of potassium to the muscles, and the method by which prostigmin lowers the amount of potassium in the muscle.

INORGANIC PHOSPHATE EXCRETION

Urine Excretion (in mgm.)

DAY OF EXPERIMENT	TIME PERIOD	MISS M.		MRS. C.	
1	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.		78.76 68.6 164.54 336.76		— 87.70 34.75 288.29
2	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.		93.18 82.94 41.33 315.06		124.98 105.73 69.54 209.30
3	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.	Prostigmin mg. 1 at 4 p.m.	— 75.07 146.64 342.4	Prostigmin mg. 1 at 4 p.m.	124.43 116.28 90.69 356.40
4	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.	K ₂ HPO ₄ added to diet.	223.49 — 438.75 376.38	K ₂ HPO ₄ added to diet.	139.78 339.08 119.39 703.30
5	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.		— 306.55 544.75 472.16		282.44 330.40 224.99 631.80
6	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.	Prostigmin mg. 1 at 4 p.m.	— 339.33 312.50 316.80		172.10 190.94 124.99 1,031.97
7	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.		— 321.24 331.22 463.09	Prostigmin mgm. 1 at 4 p.m.	126.34 287.62 188.67 653.59
8	8 a.m.-12 noon 12 noon-4 p.m. 4 p.m.-8 p.m. 8 p.m.-8 a.m.		— — — —		168.43 193.39 517.88 312.40

Fæces Excretion

DAY OF EXPERIMENT	STOOL PASSED	MISS M.	MRS. C.
1		—	—
2		—	0·696 gm.
3		—	—
4		0·437 gm.	0·738 gm.
5		0·611 gm.	—
6		0·216 gm.	—
7		}	0·601 gm.
8			—
9			0·455 gm.

Summary

Potassium balance experiments were conducted on two patients with myasthenia gravis and the effect of prostigmin on the excretion of potassium studied.

It has been shown that although the muscles liberate potassium into the blood serum after the injection of prostigmin, there is no increased urinary excretion of potassium. The potassium appears to be retained in the blood and to return to the muscles as the weakness of the muscles reappears.

My sincere thanks are due to Dr. D. Brinton and Dr. J. St. C. Elkington for allowing me to utilize the two patients on whom potassium balances were done at the National Hospital, and to the co-operation of the Nursing Staff, to Dr. McCartan of Hurstwood Park Hospital, Haywards Heath, to Mr. Harvey Jackson, F.R.C.S., and to Mr. R. Nunn, B.Sc., for his help in the estimations.

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