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Research Article

A STUDY OF THE EFFECTS OF EXCESSIVE POTASSIUM INTAKE UPON BODY POTASSIUM STORES [1]

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There is extensive evidence that provision of potassium as well as sodium may be of vital importance in the treatment of a wide variety of metabolically disturbed patients (1–3). Physicians sometimes are hesitant to administer potassium, however, because they are concerned that such therapy may result in potassium intoxication. The present studies were undertaken in an effort to gather information which would facilitate considerations of this problem.

Specifically, the aims of this study were threefold: The first was to determine the upper limit of potassium intake compatible with body potassium homeostasis. The second was to determine the nature of the variables which the body's homeostatic systems are attempting to protect under conditions of potassium loading. The third was to find out to what extent, if any, the chronically loaded individual can store surplus potassium in innocuous form when intake exceeds excretory capacity. Because these investigations of necessity involved the administration of potentially lethal doses of potassium, they have been carried out on rats rather than human beings.

MATERIALS AND METHODS

All experiments were performed on healthy male Sprague-Dawley rats weighing between 150 and 200 Gm. The animals were individually caged and provided with tap water *ad lib*. Control animals received approximately 7 Gm. of Purina rat chow per 100 Gm. of body weight per day. This provided the animal with approximately 1.6 mEq. of potassium and 0.8 mEq. of sodium per 100 Gm. of body weight per day. Potassium loaded rats were allowed 6 to 7 Gm. of the same feed in powdered form to which was added a solution containing 3.54 mEq. of potassium, 2.66 mEq. chloride and 0.88 mEq. bicarbonate per ml. This mixture was used in an effort to avoid deviations in extracellular pH which may of themselves cause shifts of potassium within the body (4). Each animal was caged separately and due attention was given to physical cleanliness. Acceptance of feed was estimated within 1 Gm. daily and potassium dosages were adjusted for changes in rat size at five day intervals. All animals were anaesthetized with intraperitoneal pentobarbital sodium prior to sacrifice. Electrocardiograms were obtained during light anaesthesia (30 mg. per Kg. body weight) with a Sanborn Twin-Beam photographic apparatus at a paper speed of 75 mm. per second and internal calibration of 1 cm. equal to 1 mV. The tracings were measured by caliper. Blood specimens for determination of plasma pH (5), carbon dioxide content (6), sodium (7), potassium (7) and chloride (8) were collected from the vena cava in heparinized syringes and delivered beneath oil for centrifugation. Immediately thereafter a representative sample of the vigorously contracting cardiac ventricles was excised, blotted free of blood and subjected to separate analysis. The intestinal tract from the esophago-gastric junction to the rectum was then removed and discarded. The heart muscle sample and the remainder of the carcass were weighed, dried to constant weight, defatted in equal parts of ethyl and petroleum ethers, dried again to constant weight and extracted with 0.75 N nitric acid for determination of sodium (7), potassium (7) and chloride (9). Cardiac chloride was determined polarographically (8) on an 0.75 N nitric acid extract of 0.3 to 0.5 Gm. of dry, defatted tissue made up to a volume of 10 ml. prior to filtering and analysis.[2]

Data for the extracellular and intracellular volumes and electrolyte distribution were calculated assuming that all chloride is extracellular and present at a concentration equal to that of an ultrafiltrate of serum.[3] In

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[2] The titration and polarographic methods for chloride were compared by application to eight samples of filtered, nitric acid carcass extract in which chloride concentration ranged between 13 and 17 mEq. per liter and to eight samples of serum in which the concentration of chloride ranged between 96 and 114 mEq. per liter. Analysis of the variance yielded a standard error of 0.358, a t value of 0.183 and a p value of 0.5.

[3] Ultrafiltrate concentration values were derived from serum concentration values by application of an assumed constant serum water value of 0.93 and a Donnan equilibrium factor of 0.95 (10).

calculating intracellular potassium concentrations, correction was made for the small extracellular potassium content of the tissues. The control electrocardiograms and serum and heart analyses carried out during the present study were supplemented by carcass analyses of normal rats of the same strain, sex, weight and dietary intake performed in this laboratory in the course of a previous study (11). In group comparisons, differences have been considered significant where the value for p is equal to or less than 0.05 using the t test.

OBSERVATIONS

Figure 1 demonstrates the relationship of the animals' potassium intake (abscissa) to the concentration of potassium in the extracellular and to the concentration and content of potassium in the total carcass and cardiac intracellular compartments. The individual control data are shown at the ordinary intake level of 1.6 mEq. of potassium per 100 Gm. body weight per day and the normal 95 per cent distribution as found for 25 animals (1.97 standard deviations) is represented by the horizontal shaded bars.

When the potassium intake was altered by 8 mEq. per 100 Gm. body weight per day stepwise increments at five day intervals, the animals refused small portions of feed on the first day of each new intake level, but otherwise remained apparently well at intakes of 9.6, 17.6 and 25.6 mEq. per 100 Gm. body weight per day. Marked diuresis and polydipsia were noted with the increasing osmotic load, but no other changes in appearance or activity were observed. A seven per cent mean weight gain occurred in these experimental animals during the course of the 15 days. Plasma potassium concentration determined in four or five animals which were sacrificed for this purpose at the end of each five day period remained within the normal range as noted in the top section of Figure 1.

When rats were subjected to the next higher dose, *i.e.*, 33.6 mEq. per 100 Gm. body weight per day, continuing partial refusal of the potassium-containing feed occurred with the result that the net potassium intake of certain rats was less than the dose offered. The animals were therefore maintained on this feeding for ten days, and were then offered a diet containing 38.4 mEq. per 100 Gm. body weight per day in an effort to attain the 33.6 mEq. per 100 Gm. body weight per day net intake level in all animals. By the 14th day of potassium loading in excess of 25.6 mEq. per 100 Gm. body weight per day, half of the 16 animals had died, each within three days of attaining its individual maximum intake (27.5 to 37.9 mEq. per 100 Gm. per day or about 60 mEq. per rat per day). The experiment was terminated at this predetermined end-point of 50 per cent deaths (LD_{50}) by the sacrifice of the eight remaining animals. These sacrificed animals had lost weight terminally to a mean of 92 per cent of initial weight and evidenced the same symptoms noted in the animals that died, namely, a progressive tendency toward roughening of coat, irritability, lethargy and eventually generalized weakness. The maximum potassium intakes in the sacrificed animals (29.4 to 37.9 mEq. per 100 Gm. per day) had also been attained between one and three days prior to sacrifice. At sacrifice, these animals had gross evidence of adrenal enlargement.

Table I shows that the plasma potassium and chloride concentration values of the LD_{50} survivors were significantly higher than those of animals on the 1.6 mEq. per 100 Gm. body weight

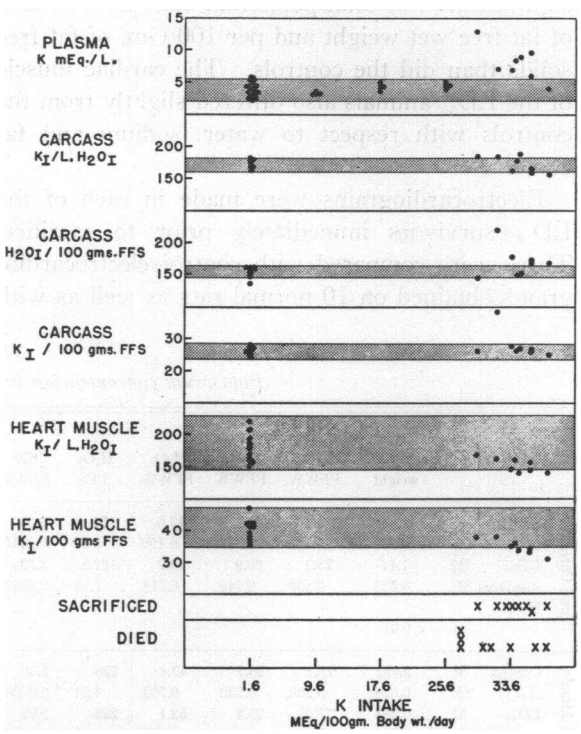

FIG. 1. RELATIONS BETWEEN K INTAKE AND EXTRACELLULAR AND INTRACELLULAR CONCENTRATION AND CONTENT VALUES

I stands for intracellular, FFS for fat free solids.

TABLE I

*Plasma concentrations**

		pH	CO_2	Cl	K	Na
Controls	M	7.43	26.7	101	4.15	143
	SE	0.0092	0.679	0.753	0.147	0.472
	N	8	8	19	25	19
LD_{50} survivors	M	7.42	27.5	108	8.0	143
	SE	0.0187	0.522	1.875	0.984	2.067
	N	8	6	8	8	8
p				0.01	0.01	

* CO_2 content, chloride, potassium and sodium are expressed as mEq. per liter of plasma. M = mean; SE = standard error of mean; N = number of animals; *p* = significance level. Plasma CO_2 was not determined in two LD_{50} survivors with plasma pH of 7.45.

per day potassium intake. However, as can be seen in the upper half of Table II, there was no significant difference between the LD_{50} survivors and the controls with respect to the total potassium content or to the concentration of potassium in cell water of the carcass as a whole.

The lower half of Table II shows that the cardiac muscle of the LD_{50} survivors contained significantly less total potassium both per 100 Gm. of fat free wet weight and per 100 Gm. of fat free solids than did the controls. The cardiac muscle of the LD_{50} animals also differed slightly from the controls with respect to water, sodium and fat content.

Electrocardiograms were made in each of the LD_{50} survivors immediately prior to sacrifice. These were compared with control electrocardiograms obtained on 10 normal rats as well as with a series gathered on rats subjected to acute potassium intoxication by intraperitoneal loading. The acute loading had resulted sequentially in bradycardia, P wave voltage depression, T wave voltage *depression* or *inversion,* PR and QT interval prolongation, QRS widening and, terminally, sine wave formation; Table III shows that the chronically loaded LD_{50} animals also showed significant changes in the first three of these variables. As can be seen in Figure 2, the changes in T wave voltage bore an inverse relation to plasma potassium concentration; there also was a statistically significant correlation between T wave voltage and potassium concentration per liter of cardiac intracellular water.

COMMENTS

In defining the ceiling, or upper limit of body tolerance for a substance, two levels may be considered: *a*) an upper lethal limit, and *b*) a lower physiologic ceiling at which pathologic alteration of body composition or concentration first occurs. It might be anticipated that the location of the intoxication zone defined by these parameters would differ among individuals as a result of biologic variability. Thus it appears from Figure 1 that the upper lethal limit for rats under the circumstances of the present experiments is between 27.2 and some quantity in excess of 38.4 mEq. per 100 Gm. of body weight per day. The fact that all but one of the LD_{50} survivors showed both hyperkalemia and characteristic electrocardiographic changes indicates that these individuals were ingesting po-

TABLE II

Potassium concentration in total carcass and cardiac muscle

			Fat % total weight	H_2O_T FFWW	H_2O_E FFWW	H_2O_I FFWW	H_2O_I FFS	Cl_T FFWW	K_T FFWW	K_E FFWW	K_I FFS	K_I LICW	Na_T FFWW	Na_E FFWW	Na_L FFS	Na_I LICW
Total Carcass	Control N=8	M	2.62	72.1	29.2	42.6	154	3.28	7.46	0.13	26.2	175	5.02	4.24	2.78	18.1
		SE	0.277	0.322	0.336	0.456	3.32	0.0445	0.0883	0.0068	0.430	1.91	0.0671	0.0421	0.225	1.4
	LD_{50} survivors N=8	M	1.11	73.1	29.9	43.2	162.8	3.52	7.67	0.23	28.0	172	5.29	4.36	3.53	21.5
		SE	0.325	0.859	0.742	0.714	7.88	0.0940	0.194	0.0270	1.56	4.60	0.1059	0.0750	0.369	1.88
		p	<0.01													
Cardiac Muscle	Control N=11	M	0.092	78.1	28.7	49.4	226	3.30	8.88	0.11	40.6	178.4	4.63	4.19	2.14	9.20
		SE	0.0184	0.200	0.650	0.702	4.21	0.0760	0.226	0.0078	1.044	7.20	0.1189	0.0800	0.602	2.39
	LD_{50} survivors N=8	M	0.288	77.2	25.2	52.1	229	2.99	8.10	0.20	35.6	152	3.90	3.56	1.49	6.38
		SE	0.0781	0.164	0.698	0.669	3.35	0.1017	0.166	0.0287	0.828	3.90	0.1321	0.0731	0.442	2.61
		p	<0.05	<0.05		<0.05			<0.05		<0.01	<0.025	<0.01	<0.005		

* Values for chloride, potassium and sodium (MEq.) and water (Gm.) are expressed per 100 Gm. of fat free wet weight (FFWW), per 100 Gm. fat free solids (FFS) and per liter of intracellular water (LICW). Subscript T = total; E = extracellular; I = intracellular.

TABLE III

Electrocardiographic standard in 10 normal male Sprague-Dawley rats weighing 150 to 200 Gm. and in the present LD_{50} survivors during light pentobarbital anaesthesia

	Controls		LD_{50} survivors		
	Mean	SD	Mean	SD	p
Ventricular rate per min.	390	14	321.9	+37.0	<0.001
P voltage, lead II, mV.	0.16	0.03	0.095	+ 0.04	<0.01
T voltage, lead II, mV.	+0.16	0.03	+0.08	+ 0.07	<0.025
PR interval, msec.	46.5	2.8	48.0	+15.0	>0.5
QT interval, msec.	56.4	3.6	51.5	+18.3	>0.5
QRS, msec.	13.8	0.7	16.8	+ 6.9	<0.4

tassium at rates which were in excess of their respective physiologic ceiling levels. The absence of diarrhea in these animals suggests that the measured intake ceilings were, in fact, indirect estimations of renal excretory capacity for potassium ion. In confirmation of this, one animal accepting 32 mEq. per 100 Gm. body weight per day was found to be excreting 97.5 per cent of this potassium in the urine.

The LD_{50} survivors appeared to be limiting their intake somewhat in accordance with their degree of hyperkalemia (*i.e.*, intoxication). Though this reaction might be considered protective in nature, it failed to prevent the spontaneous ingestion of lethal doses of potassium. Inasmuch as this phenomenon has been observed also in patients with renal failure, it appears that one cannot depend upon instinct to protect human beings against taking a lethal load of potassium by mouth in the form of fruit juice or other ordinary nutrient. Fortunately, it is possible to estimate an individual's tolerance and to prescribe accordingly (12).

The data obtained on animals taking between 1.6 and 27.2 mEq. of potassium per 100 Gm. body weight per 24 hours reveal that extracellular concentration values are strongly defended over a wide intake range. The close similarity in the carcass and cardiac values obtained on the control and LD_{50} animals indicates that the same is true also with respect to intracellular content and concentration values. It may be inferred therefore that the body's potassium homeostatic system is designed to prevent appreciable deviations in the potassium status of either the extracellular or the intracellular compartment. On the other hand, the fact that animals chronically overloaded with potassium develop electrocardiographic and other evidences of potassium poisoning in association with elevated extracellular, but normal total carcass and slightly lowered cardiac intracellular concentration and content values suggests that potassium intoxication as it occurs in normal individuals is largely an extracellular phenomenon, a conclusion reached by others on the basis of plasma and isolated muscle tissue measurements (13).

It is conceivable that these rats might have shown more of an increase in cellular potassium content had their caloric intake and hence glycogen stores been sustained by forced feeding immediately prior to death (14). Even so, however, it can be appreciated that such retention could afford only extremely limited protection under conditions of prolonged potassium loading. Moreover, the behaviour of these animals was quite characteristic of potassium intoxicated individuals who are apt to be weak and anorexic. It follows

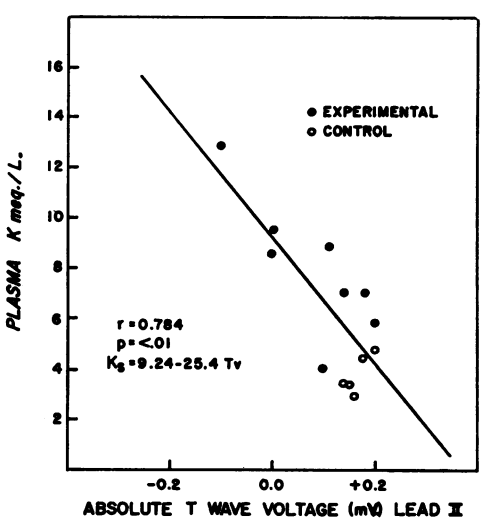

FIG. 2. RELATIONS BETWEEN ELECTROCARDIOGRAPHIC T WAVE VOLTAGE AND THE CONCENTRATION OF POTASSIUM IN PLASMA

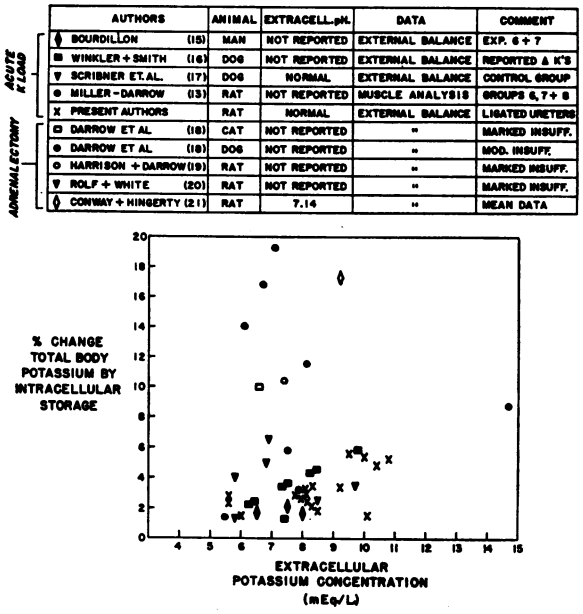

FIG. 3. PER CENT INCREASE IN CELLULAR POTASSIUM ABOVE AVERAGE NORMAL FOLLOWING ELEVATION IN EXTRACELLULAR POTASSIUM CONCENTRATION BY *ACUTE* POTASSIUM LOADING

that prevention of hyperkalemia under these circumstances depends almost exclusively upon homeostatic adjustment of renal potassium output. While this mechanism works admirably over a much wider range of intake than the normal individual is apt ever to experience, there is an upper limit to renal excretory capacity. Once this has been reached, even small increments in potassium intake in excess of maximal bodily excretory capacity can result in the production of hyperkalemia of toxic degree (12). From this interpretation, it may be concluded that the ceiling zone for potassium under conditions of chronic loading is narrow in a given individual.

The absence of intracellular potassium storage in the present chronic loading experiments is in contrast to the storage which may be observed immediately following an acute potassium load. Thus Figure 3, which presents observations on rats, dogs and man, shows that intracellular storage amounting to as much as 6 per cent of normal body potassium content may occur when the extracellular potassium concentration is abruptly elevated to 10 mEq. per liter (13, 15–22).[4] In the rat, the quantity thus stored is equal to about one quarter of the animal's usual daily intake (about 2.5 mEq. per 180 Gm. rat); in the adult human, it is equivalent to about 150 per cent of a commonplace total daily intake (about 120 mEq.). It has been found that the extra potassium stored in cells following such an acute load normally is eliminated within one to three hours (13, 25, 26). Perhaps this is fortunate, for otherwise the capacity of the cellular compartment to buffer tendencies to hyperkalemia after high potassium meals might soon become saturated.

Figure 3 also shows that the cell potassium is much higher relative to the extracellular concentration in adrenalectomized animals than in normal animals. This suggests that adrenal hormones may have a direct effect on the extracellular intracellular concentration gradient for potassium (27, 28). In view of the evidence that potassium loading is a potent stimulus to aldosterone secretion (29), the possibility arises that such adrenocortical activity may have been the factor which minimized cellular potassium storage in the body as a whole and actually caused lowering of the cardiac cellular potassium in the chronically loaded animals here reported. Because some time must elapse before the adrenals can react fully to a

[4] Data from the literature were calculated to standard units utilizing the following assumptions: *1.* Normal initial body potassium 45 mEq. per Kg. in man and appropriate normal values for dog, cat and rat tissue (23, 24). *2.* Per cent change in muscle composition reflects per cent change in total body intracellular potassium. *3.* Initial serum potassium concentration (Ks) equals 4.0 mEq. per liter when Δ concentration reported. In addition to the data shown in Figure 3 are data derived from rats identical to the control group reported in the main body of the experiment. These animals underwent ureteral ligation after a control blood sample was drawn by cardiac puncture. Within five minutes of ureter ligation, the abdomen was closed tightly and potassium was administered intraperitoneally as a 4 KCl: 1 $KHCO_3$ solution containing 0.58 mEq. potassium per ml. Dosage ranged from 2 to 6 mEq. per Kg. body weight. The animals were sacrificed at one or two hours after potassium administration by exsanguination as described. Intracellular potassium storage was calculated from the known dosages and initial and final plasma concentrations of chloride and potassium, correcting for minimal changes in weight and assuming the initial body water composition shown for control animals in Tables I and II. Plasma pH was not altered in the final blood specimen when determined in representative animals. Control animals subjected to the same procedure without the potassium load showed unaltered pH values and changes in plasma potassium concentration ranging from − 0.6 to + 0.4 mEq. per liter.

potassium load, such a mechanism would permit body cells to store potassium temporarily following an acute load, but would prevent the storage of potassium under conditions of sustained hyperkalemia. These findings also suggest that cardiac muscle may differ from other body protoplasm in its responsiveness to these adrenocortical hormones.

SUMMARY AND CONCLUSIONS

Rats subjected to loads of potassium which were increased stepwise from a normal intake level of 1.6 to as high as 36.8 mEq. per 100 Gm. body weight per day showed no signs of toxicity, electrocardiographic changes or elevation of plasma potassium concentration values until the intake exceeded 25.6 mEq. per 100 Gm. body weight per day. Of the animals taking more than this amount, one half died with signs of potassium intoxication within three days after attaining intake levels ranging between 28.8 and 38.4 mEq. per 100 Gm. body weight per day. Measurements carried out on the surviving half of the group disclosed pathologic elevation of plasma potassium concentration and characteristic electrocardiographic changes, but no significant change in total carcass potassium content or concentration values and a significant decrease in cardiac intracellular potassium concentration. These findings were in contrast to data obtained on animals on an ordinary dietary intake in which some intracellular "storage" of potassium may be observed transiently following the administration of an acute load. It is suggested that the restoration of cellular potassium values to normal levels following an acute load and the maintenance of these values at normal levels even in the presence of sustained hyperkalemia under conditions of chronic loading may be mediated by adrenocortical hormones.

It is concluded that the occurrence of sustained hyperkalemia means that the individual has surpassed the upper limit of his individual tolerance for potassium and that he probably has very little capacity to store additional potassium within the body in innocuous form.

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