Effects of Hypokalemia on Carbohydrate and Lipid Metabolism in the Rat

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SUMMARY

A study has been made of the effect of hypokalemia on carbohydrate and lipid metabolism.

Forty-two male Wistar rats, divided into three groups, were fed a low-potassium diet for two weeks. One group was injected with saline and fed a diet and drinking water supplemented with potassium, a second group was injected with desoxycorticosterone acetate (DOCA), while the third group was DOCA-treated and given potassium supplement. One week after the last injection, intracardiac glucose tolerance tests were performed, and blood and tissue specimens obtained for potassium, insulin, glucose, free fatty acids (FFA), and glycogen.

Hypokalemia, successfully induced by this regimen, was associated with: (1) retardation of growth; (2) increased liver and muscle glycogen; (3) no change in liver potassium; (4) increased fat potassium; (5) decreased muscle potassium; (6) elevation of fasting, and one- and two-hour post-glucose blood sugar concentrations; (7) no change in rate of early rapid disappearance of injected glucose; (8) no effect on fasting or post-glucose plasma FFA levels; and (9) no effect on mean fasting or post-glucose insulin levels, but a reduction in differential insulin response after glucose. DIABETES *16*:312-18, May, 1967.

The relationship between carbohydrate metabolism and the potassium ion has been under study for over four decades. In 1923 Harrop and Benedict[1] demonstrated a fall in serum potassium upon the administration of insulin, and suggested that potassium entered the liver cell along with glucose during glycogenesis. Kylin and Engel in 1925[2] showed that intravenous injection of potassium chloride lowered plasma glucose. Fenn[3] noted that the potassium content of the rat liver paralleled the glycogen content, and that deposition of liver glycogen was accompanied by an increase in hepatic potassium.

Studies of the effect of potassium depletion on carbohydrate metabolism in the rat have led to discordant results. Liver glycogen formation during injection of desoxycorticosterone acetate (DOCA) was shown to be inhibited,[4] unchanged,[5,6] or increased.[7]

Investigation of the effect of low-potassium diet on glucose tolerance have similarly yielded divergent findings: Fuhrman[8] found that eight days of a low-potassium diet had no effect on oral glucose tolerance in the rat but did cause a decrease in intravenous glucose tolerance, while Gardner et al.[9] found oral glucose tolerance unchanged after sixty days, but diabetic after ninety days, of low-potassium intake.

Other investigators have studied the relationship between carbohydrate metabolism and the potassium ion through in vitro experiments. Glycogen formation in liver slices was shown by Hastings et al.[10] to require a high potassium content in the incubation medium. Dodgen and Muntwyler[11] showed that systemic potassium depletion led to an increase in rat liver glycogen accompanied by increased liver potassium content. Because of these conflicting reports a study was undertaken of the interrelationship between induced hypokalemia, and carbohydrate and fat metabolism in the rat.

MATERIALS AND METHODS

Forty-two commercially obtained male Wistar rats were fed laboratory chow* for one week, at which time their weights averaged 180 gm. They were then divided into three groups. All animals were subsequently fed the same powdered diet, deficient in potassium but otherwise complete.†

The diet of animals in Group 1 (seven animals) was

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*"Lab Blox," purchased from Allied Mills, Inc., Chicago, Illinois.

†Purchased from Nutritional Biochemicals, Cleveland, Ohio. The stated potassium content of less than three parts per million was confirmed by analysis in this laboratory.

supplemented with 10 gm. potassium chloride per 100 gm. of diet. Their drinking water contained 1 gm. potassium chloride per 100 ml., and they received daily subcutaneous injections of 1 ml. of normal saline for one week.

Animals of Group 2 (eighteen animals) were fed the potassium-deficient diet with no supplemental potassium chloride, drank plain tap water, and received injections of 5 mg. (1 ml.) of DOCA suspension* for one week.

Group 3 (seventeen animals) were fed the potassium-depleted diet supplemented with potassium chloride, drank 1 per cent potassium chloride water, and received daily 5 mg. injections of DOCA for one week.

During the second week all animals continued on their respective dietary regimens but received no further injections. All determinations were performed at the end of the second week. After an overnight fast the rats were anesthetized with pentobarbital (5 mg. per 100 gm. body weight intraperitoneally), and light anesthesia was continued through the end of the experiment by additional injections as needed. (The hypokalemic animals were more susceptible to anesthesia: six of this group died and are not included in this report.) Thirty minutes later, 1.0 ml. of cardiac blood was drawn for the determination of potassium, glucose, and free fatty acids (FFA). Glucose (1 gm. per kg. body weight, as 50 gm. per 100 ml. dextrose in water) was then injected into the heart through the same 25-gauge needle.

Tail blood (0.3 ml.) was taken for glucose determination 5, 10, 15, 20, 25, 30, and 60 minutes after glucose injection. At the end of two hours cardiac blood was again taken for the estimation of potassium, glucose, and FFA, and the animals were killed by stunning and decapitation. Specimens of liver, rectus muscle and epididymal fat pad were removed rapidly and frozen on dry ice. Blood sugar was measured by the method of Hoffman[12] modified for the AutoAnalyzer†; FFA by a micromodification of the Dole procedure;[13] serum potassium by lithium internal standard flame photometry; muscle and liver potassium by flame photometry of ashed tissue;[14] fat potassium by flame photometry after digestion of tissue in fuming nitric acid;[15] liver glycogen by the anthrone reaction on a cold trichloracetic acid homogenate;[16] muscle glycogen by potassium hydroxide digestion and anthrone reaction on the ethanol-precipitated glycogen;[16,17] and plasma insulin by the dextran-coated charcoal immunoassay,[18] using rat insulin standard.* The fractional net rate of glucose disappearance (k, — per cent per minute) was derived from absolute glucose levels at five-minute intervals during the period ten to thirty minutes after intracardiac glucose injection, as outlined by Silverstone et al.[19] Statistical analysis was by the method of *t* test comparison of nonpaired samples.[20] Results are presented as mean values ± 1 S.E.M. (standard error of the mean).

*DOCA, purchased from Vitamix Pharmaceuticals, Philadelphia, Pennsylvania.

†AutoAnalyzer, Technicon Company, Chauncey, New York.

RESULTS

All response variables under study in the saline-treated animals (Group 1) and DOCA-injected potassium supplemented animals (Group 3) are compared in table 1. Since no difference existed between these groups by any of the criteria measured, they have been pooled and henceforth referred to as "control" for the animals rendered hypokalemic by DOCA and deficient diet (Group 2).

TABLE 1
Comparison of Groups 1 and 3

	1	3	"p"
Initial weight (gm.)	186	177	N.S.*
Final weight (gm.)	234	217	N.S.
Weight gain (gm.)	48.6	40.2	N.S.
Fasting blood sugar (mg./100 ml.)	91	85	N.S.
Blood sugar 1 hour after glucose (mg./100 ml.)	114	114	N.S.
Blood sugar 2 hours after glucose (mg./100 ml.)	106	104	N.S.
Glucose disappearance (per cent/min.)	2.05	1.96	N.S.
Serum potassium (mEq./L.)	4.0	3.9	N.S.
Muscle potassium (mEq./100 gm.)	10.25	9.11	N.S.
Fat potassium (mEq./100 gm.)	.819	.996	N.S.
Liver potassium (mEq./100 gm.)	8.55	8.96	N.S.
Muscle glycogen (gm./100 gm.)	.091	.068	N.S.
Liver glycogen (gm./100 gm.)	1.20	1.21	N.S.
Plasma free fatty acids (fasting) (mEq./L.)	1125	876	N.S.
Plasma free fatty acids (post-glucose) (mEq./L.)	1022	868	N.S.
Plasma insulin, fasting (μU./ml.)	9.8	4.3	N.S.
Plasma insulin, 2 hours after glucose (μU./ml.)	31.6	44.1	N.S.

*N.S. = Not significant, "p" > 0.05.

A. *Effect of diet and DOCA treatment on tissue and serum potassium (table 2)*

The mean fasting serum potassium concentration of the control animals was 3.97 mEq./ml., while the hypokalemic animals had a significantly ($p < .001$) lower mean serum potassium level of 2.00 mEq./L. Two

*Rat insulin, Novo Lot No. R564, was kindly supplied by Dr. B. Brodoff, New York Medical College.

hours after glucose injection serum potassium levels had risen in both groups, but significantly ($p < .001$) less in the hypokalemic animals (+0.18 mEq./L.) than in the controls (+1.28 mEq./L.).

Muscle potassium was appreciably lower in the hypokalemic animals (6.94 mEq./100 gm.) than for the control group (9.44 mEq./100 gm.). Liver potassium, however, was apparently not changed. Fat potassium was 20 per cent higher in the hypokalemic animals than in the controls ($p < .05$).

B. *Effect of hypokalemia on growth*

The hypokalemic animals initially weighed 181.0 ± 3.1 gm., and gained 8.7 ± 3.2 gm. from the time of first injection until death two weeks later. This increase, although slight, is statistically significant ($p < .02$).

Control animals weighed 179.9 ± 3.3 gm. at the start and gained 42.6 ± 2.7 gm. during the study.

C. *Effect of hypokalemia on tissue glycogen (table 2)*

Liver and muscle glycogen were significantly elevated in the hypokalemic animals, liver by 45 per cent and muscle by 106 per cent, respectively.

D. *Effect of hypokalemia on blood glucose levels and the rate of glucose disappearance (table 3)*

Blood sugar values during fasting and at one and two hours after glucose were 17 mg. per 100 ml., 17 mg. per 100 ml., and 28 mg. per 100 ml. higher, respectively ($p < .01$), in the hypokalemic animals. However, when the *fractional rate of net glucose* disappearance was derived, from absolute blood sugar values during the first thirty minutes after glucose, no difference was seen between control and hypokalemic animals ($p > 0.40$).

E. *Effect of hypokalemia on plasma FFA and plasma insulin levels*

Plasma FFA levels were somewhat reduced in the hypokalemic animals, but these differences were not statistically significant: fasting plasma FFA levels in the control animals were 944 ± 68 mEq./L. and, in the hypokalemic animals, 831 ± 50 mEq./L. ($p > 0.20$). Two hours after injection of glucose, plasma FFA values for the controls were 980 ± 88 mEq./L. and, for the hypokalemic animals, 869 ± 63 mEq./L. ($p > 0.30$).

Average fasting plasma insulin levels were slightly, but not significantly, higher in the hypokalemic animals than in the controls: 27.3 μU./ml. versus 13.1 μU./ml. ($p > 0.10$). Similarly, mean plasma insulin levels two hours after glucose did not differ between the two groups: 34.2 μU./ml. for the hypokalemic animals and 40.8 μU./ml. for the control animals ($p > 0.60$). The difference for each animal between its fasting plasma insulin level and the level two hours after glucose, however, was significantly increased only in the control group: plasma insulin levels in these animals were 27.7 μU./ml. higher ($p < 0.01$) than fasting values two hours after glucose, whereas no significant increase was noted in the hypokalemic animals (6.9 μU./ml., $p > 0.50$).

DISCUSSION

The protocol was designed to achieve hypokalemia, and depletion of body potassium stores, in an acute experiment. Since Harrison and Harrison[21] had shown that DOCA administration could induce hypokalemia, this drug was used in conjunction with a diet deficient in potassium. Initial attempts to induce hypokalemia by diet alone, by peritoneal dialysis, or by exchange resins were either unsatisfactory or too cumbersome technically. DOCA treatment was discontinued one week prior to testing to avert possible corticosteroid effects on carbohydrate metabolism, while the hypokalemic state was permitted to develop further by deficient diet alone.

Clearly, hypokalemia was achieved by the combination of DOCA and diet (Group 2), while oral potassium supplementation averted this effect (table 1).

Although no measurement was made of the extent of total body potassium depletion during the experiment, the state of body potassium stores may be estimated from the data presented here of tissue potassium content, and the size of each tissue component, as indicated by Donaldson.[22] These calculations are based on tissue obtained for analysis two hours after glucose administration and conceivably shifts of potassium subsequent to glucose administration may have occurred. However, if the fat and muscle samples were representative of all such tissue, then the following calculations indicate the extent of potassium depletion:

	Potassium Content	
	Control Animals	*Hypokalemic Animals*
Body weight	223 gm.	190 gm.
Plasma (hematocrit 50 per cent)	6.6 ml. = 0.34 mEq.	5.9 ml. = 0.13 mEq.
Liver	14.4 gm. = 1.27 mEq.	9.6 gm. = 0.79 mEq.
Muscle (45.4 per cent of body weight)	101.2 gm. = 9.55 mEq.	86.3 gm. = 6.00 mEq.
Fat (10 per cent of body weight)	22.3 gm. = 0.21 mEq.	19.0 gm. = 0.22 mEq.
	11.37 mEq.	7.14 mEq.
K^+ (mEq./kg. body weight)	50.90	37.60

These calculations would suggest a depletion of approximately 25 per cent of total body potassium by the protocol employed.

Liver glycogen was appreciably greater in the hypokalemic rats than in control animals. The induction of hypokalemia paradoxically had no obvious effect on hepatic potassium content although muscle potassium content was sharply decreased (also observed by Heppel[23] and Dodgen and Muntwyler[11]). This absence of fall in hepatic potassium concentration during hypokalemia, in the face of increased hepatic glycogen (and, therefore, also water) levels, has been taken by Fenn[3] and Dodgen and Muntwyler[11] to indicate *increased* total hepatic potassium content. Seemingly at variance with these conclusions is the work of Niedermeier and Carmichael,[5] who found a *decreased* hepatic potassium pool (expressed as milliequivalents of potassium per liver) during DOCA-induced hypokalemia. The latter authors' findings, however, may rather be an expression of the smaller liver size found as a consequence of retardation of the growth of hypokalemic animals as suggested by Donaldson[22] (table 145).

A somewhat different explanation for the failure of hepatic potassium concentrations to decline in the face of hypokalemia was offered by Buell and Turner[24] who postulated two pools of potassium. One pool, "glycogen-bound," changes in parallel with the liver glycogen content. Change in this pool is not reflected by change in liver potassium concentration, since liver water content varies in parallel with liver glycogen. A second potassium pool, labile, small and independent of changes in glycogen content, responds to changes in body potassium content. Conversely, in muscle the glycogen-obligated potassium pool is small while the labile pool is large. Since the labile potassium pool of liver is small in comparison to the large "glycogen-bound" pool, alterations in potassium content due to changes in body potassium would occur in a minor compartment and be difficult to detect.

Of considerable interest is the observation that liver and muscle glycogen increase during potassium depletion, possibly related to increased glycogenesis. Changes in eosinophil counts in potassium-depleted animals, suggesting increased adrenal cortical activity, were found by Gardner et al.,[9] while Fuhrman[8] noted increased adrenal weight in hypokalemic animals. Since adrenal cortical extracts given to normal or adrenalectomized animals result in a rise in blood sugar and increased liver and muscle glycogen,[25] increased adrenal cortical activity could result in increased gluconeogenesis and glycogenesis. Hypokalemic animals grew poorly, as was previously noted by Friedman et al.,[26] Gardner et al.,[9] and Dodgen and Muntwyler.[11] Conceivably this failure to grow may also be related to increased adrenal cortical activity, necessary amino acids being diverted from tissue synthesis into gluconeogenesis.

An effort was made in the present study to determine whether hypokalemia would affect either fasting plasma FFA levels or the "rebound" elevation of plasma FFA levels known to occur subsequent to glucose administration.[27] The possibility of such a relationship was suggested by previous studies in vitro which showed widely dissimilar effects of mono and divalent cations on lipolysis in the absence of added hormones,[28,29] and on the lipolytic response to low concentrations of growth hormone,[30] epinephrine, corticotropin and thyrotropin.[31] Although somewhat lower in the hypokalemic animals, neither fasting nor post-glucose levels of plasma FFA were found significantly altered under the circumstances of the experiments reported here.

TABLE 2

Values of serum and tissue potassium, and tissue glycogen

	Serum K^+ (mEq./L.)*			Muscle K^+ (mEq./ 100 gm.)*	Liver K^+ (mEq./ 100 gm.)*	Fat K^+ (mEq./ 100 gm.)*	Liver glycogen (gm./ 100 gm.)*	Muscle glycogen (gm./ 100 gm.)*
	Fasting	Post-glucose	Δ†					
Control	3.97 ±.05	5.25 ±.15	+1.28 ±.14	9.44 ±.37	8.85 ±.22	0.948 ±.046	1.21 ±.09	0.070 ±.016
Hypokalemic animals	2.00 ±.06	2.18 ±.12	+0.18 ±.10	6.94 ±.26	8.24 ±.38	1.143 ±.076	1.75 ±.02	0.145 ±.032
"p"	<.001	<.001	<.05	<.05	>.05	<.05	<.05	<.05

*Mean values ± standard error of the mean
Δ† = Post-glucose serum K^+—fasting serum K^+.

TABLE 3

Effect of hypokalemia on blood glucose levels and the rate of "early rapid" glucose disappearance

	FBS (mg./100 ml.)*	10-min. glucose (mg./100 ml.)*	15-min. glucose (mg./100 ml.)*	20-min. glucose (mg./100 ml.)*	25-min. glucose (mg./100 ml.)*	30-min. glucose (mg./100 ml.)*	60-min. glucose (mg./100 ml.)*	120-min. glucose (mg./100 ml.)*	"K" (—per cent/ min.)*
Control	86.5 ±4.4	256.3 ±5.7	231.9 ±4.3	213.0 ±4.7	189.9 ±4.8	171.2 ±4.8	114.2 ±2.9	103.1 ±5.2	1.99 ±.13
Hypokalemic animals	103.4 ±2.6	254.1 ±7.6	231.8 ±6.8	207.3 ±6.8	184.9 ±7.4	168.4 ±6.9	131.3 ±5.2	131.1 ±6.6	2.18 ±.20
"p"	<.01	>.80	>.90	>.40	>.50	>.70	<.01	<.01	>.40

*Mean values ± standard error of the mean

Impairment of carbohydrate tolerance by potassium depletion has been described in the rat. Gardner et al.[9] demonstrated that rats fed a synthetic diet containing 280 parts potassium per million for forty to sixty days showed no change in blood sugar levels, either fasting or four hours after the administration of peroral glucose (10 gm. per kg.), despite evident reduction of muscle potassium. Rats kept on the same diet for ninety to 120 days still maintained normal fasting blood sugar levels although the four-hour post-glucose blood sugar rose to 555 mg. per 100 ml. Fuhrman[8] found that while rats fed a low-potassium diet for eight days maintained normal fasting blood sugars and normal responses to peroral glucose, clearance of intravenously administered glucose was delayed.

In the present report, a fractional net rate of glucose disappearance was derived from the absolute plasma glucose values over the thirty minutes subsequent to glucose administration and showed no difference between control and hypokalemic animals. By contrast, Fuhrman sampled blood thirty, sixty and 120 minutes after intravenous administration of glucose and concluded that glucose disappearance was delayed. If his data are plotted on semilogarithmic paper, fractional net glucose disappearance constants are obtained of —0.77 per cent per minute for hypokalemic animals and —1.08 per cent per minute for control animals. When the data of the present report are plotted at the same time points, disappearance constants virtually identical to those of Fuhrman are derived: —0.83 per cent per minute for hypokalemic animals and —1.13 per cent per minute for control animals. The disagreement here, whether the rate of early rapid glucose disappearance has been retarded by hypokalemia, would appear to be interpretive rather than substantive. Blood sugar values determined one to two hours after parenteral administration of glucose, at a time when glucose disappearance is no longer linear, may not be a valid index of *peripheral* glucose utilization. Since net hepatic glucose release diminishes and then increases again as blood glucose levels rise above and decline below a level of about 150 mg. per 100 ml.,[32] blood sugar values at the latter end of the glucose tolerance test reflect a variable interplay between glucose uptake (hepatic and peripheral) and hepatic glucose release in response to blood sugar homeostatic regulation.[19,33] For this reason only the linear, early component of glucose disappearance has been compared in the two groups and is here referred to as the fractional net rate of early glucose disappearance. On the basis of identical, early, rapid glucose disappearance constants, it is concluded that hypokalemia did not impair peripheral glucose utilization, although elevation of "baseline" (i.e., fasting, one- and two-hour) glucose levels was observed during hypokalemia.

Goldner et al.[34] demonstrated that thiazide-induced deterioration of carbohydrate metabolism occurred in some susceptible diabetic patients. Although no connection was made at that time between hypokalemia and decreased carbohydrate tolerance, Rapaport and Hurd[35] showed that thiazide-induced glucose intolerance was reversible by potassium supplementation. Further, severe potassium loss due to diarrhea has been noted to cause profound hyperglycemia, correctable upon potassium supplementation.[36] Most recently, Conn has extended this relationship between potassium and carbohydrate metabolism in man and suggested that occult hyperaldosteronism, inducing potassium depletion, may underlie a significant proportion of abnormal glucose tolerance tests.[37]

Although elevation of the baseline glucose levels was achieved by the induction of hypokalemia (and apparently potassium depletion) in the rat, no effect was observed on the "early rapid" phase of glucose disappearance. In contrast, in man there is a more marked effect on glucose disappearance with hypokalemia.[38]

Evidence has recently been presented that potassium directly stimulates insulin release.[39] While hypokalemia

was not associated with decreased mean insulin levels (either fasting or after glucose) in the present experiment, a significant impairment in the differential insulin rise after glucose was observed for the hypokalemic animals. This is the more striking, and suggestive of a retarded or blunted insulin response to glucose in the hypokalemic animals, in view of the significantly higher level of blood sugar two hours after injection of glucose in this group.

It would appear that, in the rat, profound short-term hypokalemia may lead to mild hyperglycemia and a subtle impairment in insulin responsivity to parenteral glucose, but not necessarily to marked glucose intolerance.

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Childhood Nutrition in Lapland

T. Mellbin (Acta Paediat. *51*:Supp. 131, 1962) has published an extensive study of child health among the Swedish nomad Lapps. The survey unit was the County of Norrbotten, which lies athwart the Arctic Circle and has a population of about 260,000 (6.4 inhabitants per square mile). The nomad Lapps living in this county number only 1,700, their way of life dictated largely by the wanderings of reindeer herds. During the past two decades, children of school age have lived in special boarding schools through the school term. Altogether 450 school-age children were surveyed in this study.

Norrbotten County has seven well-equipped hospitals. There are 4.2 doctors and 15.2 nurses per 10,000 inhabitants. A great deal of medical information is presented in Mellbin's report, including genetic characteristics, congenital anomalies, incidence of parasitism, and blood counts, but this review will deal primarily with matters pertaining to nutrition and growth.

The nomad Lapps have large families, averaging 5.3 children. The mortality rate is fairly high—2.0 per cent of births during the first month of life, 5.6 per cent for the remainder of the first year, and 3.6 per cent during the ensuing fifteen years. The principal causes of death are pneumonia, meningitis and convulsions, and drownings. The mortality rate has been dropping steadily in recent years.

Dietary habits are of interest. One third of the infants are nursed beyond their first birthday; only about 30 per cent are weaned prior to six months. Solid food supplements are given early and are generally high in protein—meat, fish, and reindeer soup. Formerly reindeer milk was used for infant feeding (this remarkable fluid contains 10.3 gm. protein, 22.5 gm. fat, 2.4 gm. lactose, and 250 calories per 100 gm. milk). Berries are eaten, but relatively few vegetables, and in past years evidences of vitamin C and D deficiency were rather common. Today, about half of the school-age children show epiphyseal enlargement or curved lower legs and enamel hypoplasia is frequently seen. However, these observations are more frequent among the older children, indicating that vitamin D prophylaxis has become more widespread in recent years.

Boarding school diets were studied in great detail. The conclusion was reached that the diet was very satisfactory. Protein consumption averaged 89 gm. daily, calories 2340 daily. With the exception of niacin (9 mg. daily) the intake of all dietary constituents equaled or exceeded the National Research Council's Recommended Allowances. Vitamin D supplements were provided; otherwise, the diet alone provided adequate quantities of vitamins.

Detailed growth data are also presented. Lapp infants are somewhat smaller at birth than other Swedish infants; even so, the birth weight of 3,470 gm. and length of 51 cm. appear adequate by American standards. School-age children are shorter and stockier than their Swedish counterparts. Children residing in the northern section are shorter than those in the southern part of the county. A definite increase in height and weight has taken place during the past two decades, in keeping with the continued changes in growth rates in other parts of the world. Puberty occurs somewhat earlier in the children living in the southern part of the county. Unfortunately, no data are given for heights and weights of Lapp adults. . . .

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