J. Physiol. (1958) 141, 88–96

THE RESPONSE OF THE NEW-BORN PIGLET TO AN EXCESS OF POTASSIUM

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(*Received* 10 *December* 1957)

In experiments on the nitrogen metabolism of piglets during the first days of life (McCance & Widdowson, 1956) some of the piglets were given an evaporated cow's milk mixture. This contained more sodium, chloride and potassium than sow's milk, and piglets having it developed hypertonic expansion of the extracellular fluids. This was more fully investigated by McCance & Widdowson (1957), and it was then shown that human infants reacted in a very similar way. The animals in the first experiments also retained more potassium from the cow's milk mixture than they appeared to require for co-ordinated growth. The interest of this is not confined to piglets, for something similar has been shown to take place in human infants (M. O. Beem & C. A. Smith, personal communication). Further experiments therefore were designed to study this retention of potassium under more controlled conditions than were possible in 1956. The experiments were planned on the lines of those carried out on sodium chloride loading and are reported in this paper.

METHODS

The general arrangements were the same as those described by McCance & Widdowson (1956, 1957) and only special points need be described in detail. Three litters have been used. Each has been treated in an almost identical manner and all have given similar results. The first piglet in each litter was given water, and the second an equal volume of water to which KCl (120 m-equiv/l.) had been added. This contained the same concentration of chloride as the 0·7% NaCl solution used in the previous experiments (McCance & Widdowson, 1957). The third piglet was given a volume of sow's milk $\frac{5}{4}$ times as great as the volume of water. This made the intakes of water about equal since the sow's milk used contained 15–20% of solids. The fourth piglet was given a volume of sow's milk equal to that given to the third, but KCl was added to make the concentration of potassium in the water of the milk equal to the concentration of potassium in the water given to the second piglet. This made the potassium intake of piglets two and four about the same and roughly three times that of the third piglet, which was having sow's milk. These piglets were fed two-hourly as before. The fifth piglet was given nothing.

The experiments, like the ones on sodium chloride, lasted for 40 hr and the urines were again

collected in three periods of 12, 12 and 16 hr and analysed separately. The reducing sugar in the serum was determined by the method of Nelson (1944), and the other chemical methods have all been described before. The figures given in the tables and text are the averages of the three experiments unless it is made clear that individual results are being considered.

RESULTS

Matters of observation

At the environmental temperatures of 23–26° C at which these experiments were carried out the new-born pig appears to stand up to starvation well, and the ones given water but no food were lively and fit at the end of the 40 hr. The ones given the solution of potassium chloride in water were not so lively at the end. The hind quarters of one were paralysed for the last few hours of its life, and all four limbs of another—the cry of this animal was also weak. No other effects of raising the potassium intakes were observed visually, and in particular there was none of the pinkness and oedema so obvious when the animals were loaded with sodium chloride (McCance & Widdowson, 1957).

TABLE 1. The effects of administering KCl to piglets on the body weight, on the concentrations of potassium, sodium, chloride, urea and creatinine in the serum and on the blood sugar and haematocrit levels

Fluid administered	Water	Water + KCl	Milk	Milk + KCl	Nothing
Change in body weight (g/kg birth weight)	−111	−104	+109	+103	−111
Serum urea (mg/100 ml.)	41·8	29·3	19·8	19·2	63·5
Serum creatinine (mg/100 ml.)	1·47	1·43	1·33	1·22	1·55
Serum K (m-equiv/l.)	4·3	9·3	4·3	5·9	5·2
Serum Na (m-equiv/l.)	138	134	141	146	140
Serum Cl (m-equiv/l.)	101	106	106	109	107
Blood sugar (mg/100 ml.)	70	206	140	155	90
Haematocrit (%)	45·9	53·1	38·9	38·3	41·2

Quantitative measurements

Table 1 shows the average changes in the body weights, and the concentrations of urea, creatinine, potassium, sodium and chloride in the serum at death, the blood sugar concentrations and the haematocrits. The animals given water and the potassium solution lost about the same amount of weight, and the animals getting milk and 'potassium' milk gained weight satisfactorily and to a similar extent. Thus loading with KCl had no effect on the body weight, whether the animals were given water or milk, and this is to be contrasted with the gain of weight and extensive oedema which was induced by loading with NaCl. The addition of KCl to the water raised the serum K from 4·3 to 9·3 m-equiv/l., and its addition to the milk from 4·3 to 5·9, a much smaller increase and one not much greater than that caused by the complete deprivation of all food and water.

The serum urea was lowest in the two groups of animals fed on milk. This has been the usual experience when the piglets have been hand fed. The rise

was greatest when the animals were given nothing. The concentrations of creatinine paralleled those of urea. The blood sugars were within the normal fasting limits for adult animals in the piglets given water or in those given nothing and this has always been so at the high room temperature at which these experiments have been made (Goodwin, 1957). The blood sugar levels were much higher in the animals given the solution of potassium in water and the height seemed to vary with the extent of the paralysis. The blood sugar levels of the animals given milk were above those of the fasting animals and the addition of potassium to the milk did not make them significantly higher. The concentration of sodium in the serum was not consistently altered by the addition of KCl to the water or to the milk, but that of the chlorides was slightly raised. Laragh & Capeci (1955) found that heavy loading with potassium raised the serum sodium in dogs. The haematocrit values were

TABLE 2. The effects of adding KCl to the water and milk on the volumes of urine, the visible water balance and on the Na, K, Cl and N balances

(All results expressed per kg birth weight per 24 hr)

Fluid administered		Water	Water + KCl	Milk	Milk + KCl	Nothing
Water	Intake (ml.)	220	210	246	238	0
	Urine vol. (ml.)	234	216	169	145	30
	Visible water balance (ml.)	−14	−6	+77	+93	−30
K	Intake (m-equiv)	0	25·5	8·1	26·7	0
	Excretion (m-equiv)	3·9	22·6	1·7	16·2	3·6
	Balance (m-equiv)	−3·9	+2·9	+6·4	+10·5	−3·6
Cl	Intake (m-equiv)	0	25·7	5·3	22·5	0
	Excretion (m-equiv)	2·2	23·8	2·8	17·0	1·1
	Balance (m-equiv)	−2·2	+1·9	+2·5	+5·5	−1·1
Na	Intake (m-equiv)	0	0	3·04	3·42	0
	Excretion (m-equiv)	0·15	4·17	0·23	0·42	0·06
	Balance (m-equiv)	−0·15	−4·17	+2·81	+3·00	−0·06
N	Intake (mg)	0	0	2250	2238	0
	Excretion (mg)	214	227	270	225	143
	Balance (mg)	−214	−227	+1980	+2013	−143
	Appearing as end products (mg)	238	226	254	209	223

lowest when the animals were fed, and higher and about the same when the animals were given nothing or only water. These have been the usual findings in piglets. The piglets given the KCl in water had the highest haematocrit values in all three experiments, and this is to be contrasted with the results which followed the administration of NaCl.

Table 2 shows the visible water balances, and the potassium, sodium, chloride and nitrogen balances of the five groups of animals. The piglets given water and potassium solutions had slightly negative water balances, and the animals given nothing somewhat larger ones. The piglets which were fed had large positive water balances and loading with KCl made little difference to them. These visible water balances are in general agreement with the changes

in body weight shown in Table 1, but the effects of KCl are unlike those of NaCl, which greatly increased the retention of water. The piglets given water alone lost 3·9 m-equiv K/kg starting weight and those given the potassium solutions gained 2·9 m-equiv. Thus the bodies of animals given the KCl retained about 7 m-equiv more K/kg/24 hr than those of the animals given water alone. The piglets given milk grew well and this led to the retention of 6·4 m-equiv K/kg/24 hr. The animals getting the 'potassium' milk had, however, larger positive balances, amounting to 10·5 m-equiv/kg/24 hr, so that at death they had retained about 4 m-equiv more K/kg/24 hr than their littermates given normal milk. The animals given nothing lost 3·6 m-equiv K/kg/24 hr, which agrees very well with the losses sustained by the animals having water.

The potassium was given as the chloride so that the animals getting the KCl had large intakes of chlorides. These chlorides were, however, more completely excreted than the potassium, and the large retentions which followed the administration of NaCl in the previous experiments must be attributed entirely to the retention of the sodium ion. This appears also to be so in human cardiac failure (Friedberg, 1957). The piglets getting water alone had very small negative sodium balances. This is usual in piglets and agrees with the findings in the animals given nothing at all. The negative balances were materially increased by the addition of potassium chloride to the water in all three experiments. Laragh & Capeci (1955) did not find this in adult dogs. The piglets getting milk had small positive sodium balances associated with true growth, and this was not affected by the addition of potassium to the food.

The negative nitrogen balances were least in the animals given nothing at all. This result has been obtained and discussed before. The negative balances on water and on potassium solutions were of the same order and so were the amounts of nitrogen appearing as end products of metabolism. There was no valid evidence of the nitrogen-sparing effect which followed the administration of NaCl. The animals given milk and 'potassium' milk both had large positive balances due to growth, and incorporated the usual 85–90% of their ingested protein N into their tissues. The nitrogen appearing in the form of end products (calculated from the change in serum urea and the total nitrogen excreted) was less when the animals were given 'potassium' milk than when they were given normal milk. This was largely due to one animal which gave a surprisingly low result and the difference shown in the table may not be a real one.

Table 3 shows the composition of the skeletal muscles, liver and heart, and the weights of the two last as percentages of the body weight at death. Loading with KCl made no difference to the percentage of water in the tissues at death, and analysis of the carcasses confirmed this. Loading with NaCl always raised the percentage (McCance & Widdowson, 1957). The reduced amounts of water in the livers of the animals which were fed is a confirmation of previous results.

The administration of the potassium chloride led to an increase in the potassium in skeletal muscle from 75·4 to 91·7 m-equiv/kg when the animals were not fed, and from 69·2 to 74·0 when the animals were fed. There was no corresponding increase in the percentage of nitrogen, and consequently a fall in the N:K ratio in both groups of animals given potassium. In the liver and heart the effects of giving potassium were smaller and somewhat equivocal. This was not unexpected in the light of work which has been carried out on potassium deficiency (Gardner, Talbot, Cook, Berman & Uribe, 1950). Its administration made no difference to the weight of the liver. The increased size of the organ in the animals which were fed—both absolutely and as a percentage of the

TABLE 3. The effect of administering KCl to piglets on the concentration of K, Na, Cl and N in the tissues

Fluid administered	Water	Water + KCl	Milk	Milk + KCl	Nothing
Muscle					
Water (g/100 g)	85·1	84·5	84·0	84·0	84·9
K (m-equiv/kg)	75·4	91·7	69·2	74·0	75·5
Na (m-equiv/kg)	39·0	30·7	45·8	46·9	45·3
Cl (m-equiv/kg)	36·6	41·8	38·7	37·5	40·6
N (g/100 g)	1·51	1·47	1·46	1·44	1·61
N (mg/m-equiv K)	20·0	15·9	21·0	19·5	21·3
Liver					
Weight (% of body wt.)	2·20	2·24	4·24	4·52	2·29
Water (g/100 g)	80·1	80·0	76·4	77·3	80·9
K (m-equiv/kg)	80·9	82·5	70·2	75·6	70·7
Na (m-equiv/kg)	47·1	41·0	41·8	39·9	54·3
Cl (m-equiv/kg)	50·5	46·5	42·4	39·5	53·7
N (g/100 g)	2·28	2·23	1·63	1·55	2·28
N (mg/m-equiv K)	28·2	27·0	23·2	20·5	32·3
Heart					
Weight (% of body wt.)	0·72	0·68	0·73	0·68	0·64
Water (g/100 g)	83·2	82·9	82·9	82·9	83·1
K (m-equiv/kg)	77·2	84·3	80·3	78·4	82·1
Na (m-equiv/kg)	45·2	40·2	42·3	43·6	45·1
Cl (m-equiv/kg)	40·0	46·7	38·8	42·3	39·7
N (g/100 g)	1·89	1·94	1·80	1·80	1·81
N (mg/m-equiv K)	24·5	23·0	22·3	23·0	22·1

body weight—has been observed and reported before (McCance & Widdowson, 1956). The hearts of the animals which were given potassium were somewhat smaller than their controls but the differences may have been due to chance. The concentration of potassium in the organ was not consistently raised by potassium administration although it would appear to have been so when the animals did not get milk.

DISCUSSION

Although there are minor points of uncertainty the main results are clear, and only these will be discussed.

Electrolyte balances

Chloride ions were freely excreted by the new-born piglet unless the accompanying cation was retained, and the kidney of the new-born piglet has a

much greater capacity for excreting potassium ions than sodium ions. The work of Tudvad, McNamara & Barnett (1954) and of McCance & Widdowson (1957) suggests this is true also of the human infant. Nevertheless, the potassium ions were not completely excreted, and rose to concentrations in the extracellular fluid which were toxic in the group of animals which received the solutions of potassium chloride in water. According to Black (1957) 'an absolute increase in the K content of the body is probably rather uncommon, and has not been adequately demonstrated'. These experiments would appear to have done so if it has not been done before, for the animals which were *not* fed retained 7 m-equiv more K/kg/24 hr than their controls, and those which *were* fed 4 m-equiv. The administration of potassium chloride brought about no increase in the total amount of water in the body or changes in the over-all metabolism of protein. There can hardly have been any expansion of the extracellular fluids and these could have accommodated less than 1 m-equiv K/kg body wt./24 hr. Since, moreover, the retentions of potassium considerably exceeded those of chloride we may infer that most of the potassium was taken up by the cells. In the skeletal muscles this was certainly so. If all the chloride in this tissue is assumed to be extracellular it may be calculated from the figures given in Table 3 that 14·3 of the 16·3 m-equiv of surplus potassium found in each kg of the skeletal muscles of the animals given the potassium chloride in water were in the cells and 4·4 of the 4·8 m-equiv of the surplus potassium found in each kg of the skeletal muscles of the animals given the potassium chloride in the milk were likewise in the cells. The skeletal muscles, moreover, accounted for a large fraction of the surplus potassium retained by the whole animal, but exact calculations cannot be made. Storage in this site is generally regarded as the fate of most of the potassium retained by the body after its administration (Fenn, 1940; Fenn, Noolan, Mullins & Haege, 1941–2; Grob, Johns & Liljestrand, 1957; Grob, Liljestrand & Johns, 1957). The capacity to absorb and retain potassium in excess of its anticipated requirements has been encountered by M. O. Beem & C. A. Smith (personal communication) when the intakes have been raised and the present experiments show in an exaggerated form the internal changes which probably took place.

The blood sugars

The animals given the potassium chloride in water had high concentrations of sugar in the blood when they were killed after 40 hr starvation. This is a finding worth remark, for unfed new-born piglets tend to become hypoglycaemic, especially if they are cold (Goodwin, 1957). Hyperglycaemia does not seem to have been recorded in patients suffering from paralysis due to potassium intoxication, perhaps because estimations of the blood sugar have not been made before giving the large amounts of glucose which now constitute part of the treatment (Winkler, Hoff & Smith, 1941; Finch, Sawyer & Flynn,

1946; Govan & Weiseth, 1946; Merrill, Levine, Somerville & Smith, 1950; Bull, Carter & Lowe, 1953; Nadler, 1953; Gamstorp, Hauge, Helweg-Larsen, Mjönes & Sagild, 1957). This observation of raised blood sugar makes one think of the hyperglycaemia reported by Silvette (1938) and his associates (Silvette, Britton & Kline, 1938) to follow injections of potassium salts. Since these authors emphasized the difference they had found between the responses of different species, this may explain why the effect has not been noted in human beings, and why Odashima (1931–2) did not observe it in rabbits. The only experiments on man with any bearing on this matter seem to be those of Thompson & McQuarrie (1934), who found in controlled work on a diabetic child that heavy doses of potassium chloride greatly increased the output of glucose in the urine. Before this time doses of potassium salts had been claimed to lower the blood sugar in diabetes (Semler, 1925), but the results obtained were quite unconvincing. The rise in blood sugar may be due to the effect of potassium salts on the liberation of adrenalin (Fenn, 1940). It seems less likely to be due to the kind of effects which have been observed in tissue slices or portions of rat's diaphragm respiring *in vitro* in media containing concentrations of potassium far above the physiological ranges possible in an extracellular fluid during life (Clarke, 1955; Ashmore, Cahill, Hastings & Zottu, 1957; Cahill, Ashmore, Zottu & Hastings, 1957).

Homoeostasis and growth

The importance of growth as an agent in homoeostasis during the new-born period has been demonstrated and discussed before (McCance & Widdowson, 1956, 1957), but mainly as it applies to nitrogen metabolism. The present results show its importance in another way. The animals getting the potassium in their milk were able to grow, and although this did not prevent some rise taking place in the potassium in their sera and muscle cells, they grew perfectly normally so far as could be observed, and exhibited no signs of paralysis or the high blood sugars so obvious in the animals given the same amount of potassium but without the means by which to grow. It is worth noting in this connexion that when the potassium was given in water the retention of 2·9 m-equiv K/kg starting weight produced paralysis and widespread signs of toxicity in 40 hr, whereas the same amount of potassium in milk was followed by a retention of 10·5 m-equiv K/kg and signs of good health. It is possible that withholding all food on the eleventh day while maintaining the infusion containing the potassium salts was what precipitated the potassium intoxication in the infant reported by Govan & Weiseth (1946). There may be other examples of this kind of thing in the literature but it is unnecessary to labour the point. It is evident that potassium infusions should be given with greater care in a starving than in a growing infant, and the protection afforded by food may not be confined to its effects on growth, for the storage of glycogen at all

ages is accompanied by the deposition of potassium and water (Calkins, Taylor & Hastings, 1954) and greater care should therefore be taken over potassium infusions in adults if they are being given without, rather than with, glucose.

SUMMARY

1. Piglets have been given the following by stomach tube two hourly for the first forty hours of their lives (1) water, (2) water and KCl, (3) sow's milk, (4) sow's milk and KCl, and (5) nothing.

2. Most of the KCl was excreted, but the administration of KCl in water led to progressive retention of K, paralysis and raised blood sugar.

3. The animals getting KCl in milk retained a mild excess of K but growth, which was normal, completely protected them from toxic effects.

4. The serum, urines and tissues have been collected and analysed and the results reported in tabular form.

We are grateful to Stan and Terry Cowen for their care of the animals and help over the day and night work involved in these experiments.

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