Hyperglycemia, Hypoinsulinemia, and Hyperglucagonemia in Acute Water Intoxication

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SUMMARY

When acute (four-hour) hyponatremia with clinical signs of water intoxication was produced in normal weanling mice by the use of hypotonic glucose or deionized water, there was a two-to-fourfold increase in plasma glucose concentration. Concomitantly, concentrations of plasma insulin fell 63 to 68 per cent, whereas plasma glucagon increased to 262 per cent of control. The findings are compatible with stress-induced catecholamine release. DIABETES *27*:61-63, January, 1978.

We have recently found that acute hyponatremia induces hyperglycemia. This observation was uncovered during an investigation of the effects of water loading on cerebral metabolism in young mice.[1] Acute water intoxication was produced by the use of hypotonic solutions of glucose or fructose. When plasma Na^+ concentration was reduced to amounts associated with neurologic dysfunction, plasma glucose concentration was more than twice that of the controls. The rise of plasma glucose levels was attributed to the use of the carbohydrate-containing solutions. Since the hyperglycemia complicated the interpretation of the effects of hyponatremia per se on brain carbohydrate and energy metabolism, attempts were made to reduce plasma Na^+ levels by the use of hypotonic hexose-free solutions. Subcutaneous injections of 0.45 per cent NaCl did not lower plasma Na^+ concentration, and the effects of 0.22 per cent NaCl were inconsistent; therefore, it was necessary to resort to the use of deionized water. Surprisingly, the resulting hyponatremia was associated with a doubling of plasma glucose concentration. This report is a preliminary study of the mechanism of this finding.

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METHODS

Preparation of Animals

Litters of normal nursing 17-to-23-day-old Swiss-Webster mice were used (average weight 12 gm.). In each litter, control and experimental animals were carefully matched by weight. Acute water intoxication was produced by three injections of 2.5 per cent glucose in water or two injections of deionized water (each dose 100 ml./kg.). Two types of controls were used: one group of animals received two or three injections of 0.9 per cent NaCl, and the other received three injections of 2.5 per cent glucose in 0.9 per cent NaCl. Injections were given subcutaneously at 80-minute intervals. Animals were killed by decapitation. Blood was quickly collected from the severed neck vessels in heparinized microtubes (Caraway).

Preparation of Plasma

Blood was centrifuged promptly in a cold room at 4°. Fresh plasma was used for Na^+, K^+, insulin, and glucagon measurements. For glucose determination, plasma was deproteinized with 20 volumes of 0.5 M perchloric acid. It was not necessary to neutralize the supernatant fluid since the volume of extract required for the assay (2 μl. in 1 ml. of reagent) did not change the pH of the buffer or affect the complete recovery of the standards.

Analytic Methods

Plasma Na^+ and K^+ concentrations were measured in a flame photometer. Plasma glucose was assayed in a Farrand fluorometer with $NADP^+$, hexokinase, and glucose-6-phosphate dehydrogenase.[2]

TABLE 1

Effect of hyponatremia on plasma glucose and electrolyte levels

Measurement	Treatment			
	0.9% NaCl*(10)†	2.5% Glucose in 0.9% NaCl (10)	Deionized water (8)	2.5% Glucose in water (6)
	mean ± S.E.M.			
Na^+, mEq./L.	144 ± 1	146 ± 1	107 ± 3‡	97 ± 1‡
K^+, mEq./L.	7.8 ± 0.2	7.5 ± 0.2	8.3 ± 0.3	8.4 ± 0.2
Glucose, mM	9.34 ± 0.38	8.44 ± 0.60	18.2 ± 1.9‡	38.2 ± 1.9‡

*Findings in controls that received two injections of 0.9 per cent NaCl were not significantly different from those seen in animals that received three injections (see METHODS); therefore, results were pooled.

†Number of animals is given in parentheses.

‡p vs. 0.9 per cent NaCl <0.01.

Plasma insulin and glucagon were assayed by double-antibody procedures.[3,4]

For the three variables shown in table 1 (plasma Na^+, K^+, and glucose) three experimental groups were compared with the control (0.9 per cent NaCl). Statistical analysis of these data was performed with Dunnett's multiple-comparison test.[5,6] For the two variables shown in table 2 (plasma insulin and glucagon) the significance of the differences between the control and experimental animals was established on Student's *t*-test.

RESULTS

"Clinical" Comment

Animals treated with deionized water began to exhibit abnormal neurologic signs shortly after the second injection (80 minutes). In hypotonic-glucose-treated animals, symptoms of water intoxication were not apparent until after the third injection (160 minutes). There was muscle weakness, as evidenced by decreased spontaneous activity and splaying of the posterior extremities; in more severe cases, there was a loss of righting reflexes and coma.

Hemolysis was evident in about 20 per cent of the animals treated with subcutaneous injections of deionized water. Animals that exhibited hemolysis were not studied further. No hemolysis was evident in any of the animals treated with 2.5 per cent glucose in water.

Treatment with deionized water reduced plasma Na^+ concentration 26 per cent and doubled plasma glucose concentration (table 1). Concomitantly, plasma insulin was reduced 63 per cent (0.71 ± 0.28 ng./ml., n = 8, vs. 1.91 ± 0.23 in controls (table 2), p = 0.002).

Effect of Acute Water Intoxication in Blood

When acute water intoxication was produced by the use of 2.5 per cent glucose in water, plasma Na^+ concentration was reduced 33 per cent (table 1); this decrease was significantly greater than that found in water-treated mice, p = 0.011. It is possible that the difference is due to the larger total volume of solution injected (300 ml./kg. vs. 200 ml./kg. in water-treated mice, see METHODS). The fourfold increase in plasma glucose concentration was associated with a 68 per cent decrease in plasma insulin and 262 per cent increase in plasma glucagon levels (table 2). It is of interest that in littermates that received 2.5 per cent glucose in 0.9 per cent NaCl rather than in water, plasma Na^+, K^+, and glucose levels were unchanged (table 1), and the mean plasma insulin level, 1.92 ± 0.31 ng./ml. (n = 10), was almost identical to that seen in controls that received 0.9 per cent NaCl (table 2).

DISCUSSION

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TABLE 2

Effect of hyponatremia on plasma insulin and glucagon concentrations

Measurement	Treatment		p value
	0.9% NaCl	2.5% Glucose in water	
	mean ± S.E.M.		
Insulin, ng./ml.	1.91 ± 0.23 (10)*	0.62 ± 0.10 (6)	0.001
Glucagon, pg./ml.	333 ± 47 (7)	1,206 ± 192 (4)†	<0.001

*The number of animals is given in parentheses; it was not possible to obtain sufficient plasma for both insulin and glucagon levels in all the animals used for table 1. Plasma insulin concentrations in animals treated with deionized water and 2.5 per cent glucose in 0.9 per cent NaCl are given in the text (there was insufficient plasma to measure glucagon in these mice).

†One value of 301 pg./ml. was not included.

stress, such as fulminating bacterial infection,[7] acute myocardial infarction,[8] and application of noxious stimuli,[9] hyperglycemia was associated with increased plasma glucagon levels but without a significant change in plasma insulin concentration.[7-9] In our young mice the hyperglycemia induced by acute water intoxication appears to be due to the concomitant elevation of plasma glucagon and depression of plasma insulin.[10] Hyperglycemia, hypoinsulinemia, and hyperglucagonemia are consistent with an increased secretion of catecholamines—either directly from noradrenergic nerve terminals on the islet cells of the pancreas and/or from an increased release of epinephrine from the adrenal glands.[11,12] However, there are other possibilities: For example, hyponatremia itself may inhibit insulin release and augment glucagon secretion; nor are the effects of hyponatremia and hypoosmolarity on peripheral glucose utilization or glucose production known. We have previously reported that acute water intoxication produces metabolite changes in brain that indicate reduced cerebral glucose utilization.[1] Future research studies will attempt to elucidate the mechanism(s) of the findings.

During the preparation of this report an article appeared supporting the association of hyperglycemia with severe hyponatremia in dogs.[13] After one or two hours of extracorporeal perfusion with 5 per cent glucose in water during cardiopulmonary bypass, concentrations of plasma Na^+ fell from 157 to 91 mEq. per liter and those of plasma glucose increased from 8 to 123 mM. To our knowledge, the association of hyperglycemia with hyponatremic syndromes in human beings has not been reported previously. This may be due to the fact that acute lowering of plasma Na^+ to the amount produced by the experimental procedures would rarely be seen in clinical practice. On the other hand, the correlation of significant elevation of plasma glucose with reduced plasma Na^+ concentration may not have been fully appreciated previously.

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