

# Glucose Intolerance in Hypernatremic Rats

Menachem Nitzan, M.D., and Sophia Zelmanovsky, M.Sc., Petah Tikva, Israel

## SUMMARY

A study has been made of the effect of hypernatremia on carbohydrate metabolism in the rat. It was shown that rats rendered hypernatremic by subcutaneous injections of hypertonic sodium solutions manifest increased fasting blood glucose levels, as well as a decreased ability to dispose of an exogenous glucose load.

The mechanism by which hypernatremia alters carbohydrate metabolism has not been determined. However, an impairment of normal cellular functions known to accompany hypertonicity of body fluids as well as disturbed secretion of the hormones which regulate carbohydrate metabolism, could explain the metabolic abnormality. *DIABETES* 17:579-81, September, 1968.

The simultaneous occurrence of hyperglycemia and hypernatremia has been reported in several disease states. These include unregulated diabetes mellitus,<sup>1</sup> ketoacidotic diabetic coma,<sup>2</sup> nonketotic hyperosmolar diabetic coma,<sup>3</sup> severe burns,<sup>4</sup> acute intracranial injuries<sup>2</sup> and hypernatremic dehydration secondary to acute gastroenteritis in infancy and childhood.<sup>5,6</sup>

The high blood sugar levels which are often observed in the latter condition suggest the possibility that hypernatremia itself may interfere with carbohydrate metabolism.

The present study was designed to evaluate the importance of hypernatremia of the degree encountered clinically, as a cause or a contributory factor in glucose intolerance.

## MATERIALS AND METHODS

*Animals:* The experiments were carried out on male rats of a locally bred Swiss albino strain weighing from 140 to 160 gm. at the beginning of the experimental

period. Prior to the study, water and food (Purina Rat Chow) were allowed ad libitum.

*Experimental procedure:* Two groups, each comprising sixteen rats, were designated. The animals were injected subcutaneously with 4.5 ml. of either hypertonic (Group A) or isotonic (Group B) solution of sodium. No obvious signs of local inflammation were evident following the subcutaneous injection of the hypertonic solution. This volume was divided into two equal doses with a five-hour interval between them. The solutions contained the following concentrations of ions in mEq. per liter.

	Na	Cl	HCO <sub>3</sub>
Hypertonic	1,500	1,000	500
Isotonic	150	100	50

The animals were weighed before the first injection and twenty-four hours thereafter, before being subjected to glucose tolerance test. During this period they had no access to food or water. After taking 0.1 ml. fasting blood samples from the cut tip of the tail for glucose determination, each rat was injected with 3.5 ml. of a 10 per cent glucose solution per 100 gm. of body weight intraperitoneally. Blood samples were taken 60 min. (0.1 ml. tail blood) and 120 min. (exanguination via the abdominal aorta under light ether anesthesia) after glucose administration. Diabetic indices ( $I_D$ ) were determined using the formula of Coupland, Davidson and Lazarow.<sup>7</sup>

$$I_D = \frac{60 \text{ min. experimental BG}}{60 \text{ min. average normal BG}} \times \frac{120 \text{ min. experimental BG}}{120 \text{ min. average normal BG}}$$

For this purpose the 60 min. and 120-min. glucose levels of the control rats were regarded as normal average values.

*Analytical methods:* Three specimens of 0.1 ml. of blood from each animal (time 0, 60 and 120 min.) were promptly deproteinized with Ba(OH)<sub>2</sub> and ZnSO<sub>4</sub> and analyzed for glucose content by the glucose oxidase method of Kingsley and Getchell.<sup>8</sup> The following additional determinations were performed on the samples drawn from the abdominal aorta: Clay Adams heparinized tubes were used to measure the hematocrit, urea was estimated by the method of Rappaport,<sup>9</sup> sodium and potassium were determined by flame photometry (Baird

From the Department of Pediatrics and Laboratory for Pediatric Research, Rogoff-Wellcome Trust Medical Research Institute, and Biochemical Section of Rappaport Laboratories, Beilinson Medical Center, Tel Aviv University Medical School, Petah Tikva, Israel. Dr. Nitzan's present address is: Department of Medicine, Section of Endocrinology, Metabolism and Nutrition, Northwestern University Medical School, Chicago, Illinois 60611.

Atomic Inc. Model KY-1), chloride by the titration method of Schales and Schales,<sup>10</sup> and pH and PCO<sub>2</sub> were determined on an Astrup apparatus.

## RESULTS

The pertinent experimental data are summarized in table 1. The osmotic diuresis caused by hypertonic solution of sodium resulted in a significantly greater mean weight loss in the hypernatremic rats (Group A), 13.4±0.45 (SEM) per cent, than in the controls (Group B), 8.9±0.41 per cent. Nevertheless, the two groups did not differ with regard to their hematocrit values, a fact which may be accounted for by dehydration of the intracellular space and expansion of the extracellular compartment of the body. As expected, the rats included in Group A were found to have significantly higher values of sodium and chloride than those

twenty-four-hour fast, as well as the mean glucose levels 60 min. and 120 min. after the glucose load, were significantly higher in the hypernatremic group, 87±3.1, 182±3.9 and 165±3.5 mg. per 100 ml. respectively, than in the control group, 78±1.9, 137±3.2 and 117±3.8 mg. per 100 ml. respectively. The mean diabetic index of Group A was 1.87±0.078, a value which should be regarded as subdiabetic according to the criteria of Lazarow.<sup>11,12</sup>

## DISCUSSION

The results of the present experiment, indicate that hypernatremia of the degree encountered clinically, may be associated with abnormal carbohydrate metabolism. The higher glucose concentration in the hypernatremic animals following the exogenous glucose load, cannot be accounted for by the relatively smaller volume of distribution, nor can it be explained by the uremia of the degree found in these animals, which is known to accompany hypernatremia.<sup>2</sup> On the other hand, there is reason to suspect that intracellular potassium depletion which may be present in hypernatremic states<sup>13</sup> contributes to the abnormal glucose metabolism.<sup>14</sup>

When osmotic imbalance is created by an injection of hypertonic sodium solution, there are three ways in which osmotic equilibrium may be achieved: water may leave the cell; sodium ions may enter the cell; and there may be a change of cellular constituents to increase osmolar concentration either by dissociation of bound electrolytes or by breakdown of complex polyvalent ions.<sup>15</sup> Such events may well disturb the normal cellular metabolism. There is evidence that hypertonicity can alter the metabolic function of isolated tissues and subcellular particles.<sup>16,17</sup> Kean et al.<sup>16</sup> have found that the rate of glycolysis in renal slices is inhibited progressively as osmolality of the bathing medium is increased. These in vitro experiments, as well as the clinical observations that high blood sugar levels frequently occur in hypernatremic dehydration,<sup>5,6</sup> concur with our findings and lend further support to the assumption that carbohydrate metabolism may be adversely affected by hypertonicity of the body fluids. On the other hand, hyperosmolarity has been reported to stimulate glucose uptake and C-14-incorporation from C-14-labeled glucose into CO<sub>2</sub>, in rat adipose tissue and diaphragm in vitro.<sup>18</sup> In view of this observation, the possibility that the hypernatremic glucose intolerance, which was found in vivo, might be causally related to a disturbed secretion of the hormones which regulate carbohydrate metabolism, should also be considered.

TABLE 1  
Experimental data

	Group A (hypernatremic)	Group B (control)	P <
Weight loss per cent	13.4±0.45 (16)	8.9±0.41 (16)	0.001
Hematocrit per cent	48±1.2 (12)	46±1.3 (12)	NS
Sodium mEq./L.	159±0.9 (16)	141±0.8 (16)	0.001
Potassium mEq./L.	4.6±0.23 (16)	5.0±0.15 (16)	NS
Chloride mEq./L.	119±1.4 (16)	103±0.9 (16)	0.001
pH	7.36±0.014 (8)	7.39±0.009 (8)	NS
PCO <sub>2</sub> mmHg.	34.0±1.36 (8)	35.9±1.28 (8)	NS
Urea	66±2.3 (16)	49±1.8 (16)	0.001
Glucose mg. per 100 ml. (0 min.)	87±3.1 (16)	78±1.9 (16)	0.02
Glucose mg. per 100 ml. (60 min.)	182±3.9 (16)	137±3.2 (16)	0.001
Glucose mg. per 100 ml. (120 min.)	165±3.5 (16)	117±3.8 (16)	0.001
Diabetic index	1.87±0.078 (16)		

Values given are means ± S.E. of the mean for the number of determinations indicated in parentheses.

NS = not significant by Student test ( $p > 0.05$ ).

of Group B. Except for higher urea levels in the hypernatremic animals than in the control animals, there was no evidence of other significant intergroup differences as far as the composition of the internal environment was concerned.

The initial mean blood glucose level following a

In this connection, it is of interest to note that the injection of hypertonic sodium solutions into dogs is followed by cardiovascular changes characteristic of sympathicomimetic effect.<sup>19</sup> The demonstration of a hypotensive response to the intravenous injection of phentolamine<sup>20</sup> suggests the appearance of circulating catecholamines following intra-arterial injection of hypertonic solution.

In addition, since hypernatremia may cause injury to the central nervous system,<sup>15</sup> further studies will be necessary to determine whether lesions of the hypothalamus play a role in the production of the glucose intolerance.<sup>2</sup> Whatever the mechanism involved, our findings suggest that hypernatremia as such may have a diabetogenic effect. Whether this effect is related in a dose response fashion to the elevation of the plasma sodium, still remains to be investigated. Our observation may have a bearing on clinical conditions in which hyperglycemia and hypernatremia occur simultaneously. Hypernatremia could act as a primary factor causing glucose intolerance, or could lead to further worsening of an already existing abnormality in carbohydrate metabolism.

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