Mechanisms of Disturbances of Carbohydrate Metabolism in Altered Acid-Base States

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Glucose homeostasis is known to be maintained by nervous and humoral stimuli, the most important among them being the blood insulin level. Any pathological state affecting insulin or antiinsulin hormone secretion may result in disturbances of glucose metabolism. One of the processes characterized by drastic changes in the organism's hormonal status is a disturbed acid-base balance (ABB). Acute metabolic acidosis is known to raise the blood insulin level [3,4,10] as well as to increase its binding in tissues [2], leading to resistance to insulin [7], whereas glucagon binding in tissues is decreased [2]. On the contrary, acute metabolic alkalosis leads to a drop of the insulin and a rise of the glucagon blood levels [4]. A drop of the intracellular pH in pancreatic islet cells enhances their electrical activity [12] and insulin secretion [9]. The influence of the pH on β cells is probably mediated by changes in the intracellular K^+ and Ca^{2+} concentrations [8,11,13]. Acidosis might be expected to cause hypoglycemia and enhanced glucose tolerance. However, in chronic acidosis, just as in chronic alkalosis, fasting hyperglycemia is observed together with a diabetoid nature of the sugar curves [1].

The aim of the present study was to investigate the nature and endocrine mechanisms underlying the disorders of glucose metabolism during chronic ABB disturbances.

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MATERIALS AND METHODS

Experiments were carried out on 100 intact and hypophysectomized albino male rats weighing 120-180 g. Alkalosis and acidosis were induced by intragastral administration of 20 mmol/kg body weight ammonium chloride or 27 mmol/kg sodium hydrogen carbonate, respectively. These solutions were administered to intact animals over 6 days and to hypophysectomized rats over 3 days. One hour after the last injection the fasting and post-double glucose load (2 g/100 g body weight) blood sugar levels were measured with Lachema kits (Czechoslovakia). For a study of the hormone content a group of animals was decapitated one hour after the first or the last intragastral saline administration. Blood was collected and the plasma hormone levels were measured using the following RIA kits: Biodata (Italy) for glucagon, CIS (France) for corticotropin, and IBOC (Belarus) for insulin assay. Statistical processing of the results was performed using the Student *t* test.

RESULTS

As in our previous experiments [1], the long-term shifts of ABB in both the acidic and alkaline directions led to fasting hyperglycemia and to a two-bell shape of the sugar curves after the double glu-

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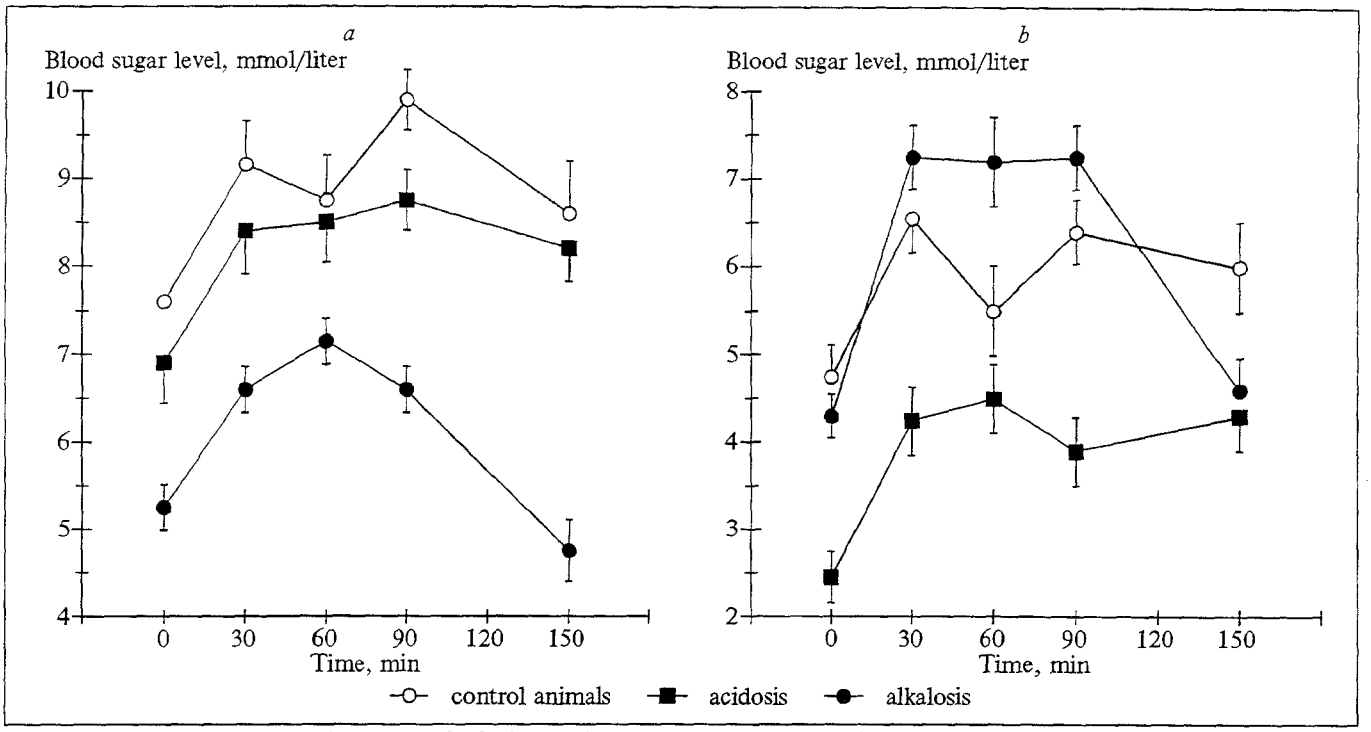

Fig. 1. Effect of chronic acidosis and alkalosis on glycemia curves in intact (*a*) and hypophysectomized (*b*) rats.

cose load (Fig. 1, *a*), the reduced glucose tolerance being more pronounced in chronic alkalosis.

The study of the blood hormone levels (Table 1) showed that the diabetes-like sugar curves are attributable to a decrease of the insulin content by 28.7% and 46.9% in chronic acidosis and alkalosis, respectively. The more pronounced fasting glycemia in both acidosis and alkalosis is also related to enhanced activity of the hypothalamic-hypophyseal-adrenal system (HHAS), which manifests itself in an elevated corticotropin concentration. In alkalosis the glycemia level is also augmented, due to enhanced glucagon secretion. Unlike in acute alkalosis, in acute metabolic acidosis the blood insulin level has been shown [4] to rise in parallel with the corticotropin content. The drop of the insulin level after the acidosis turns into a chronic form is apparently caused by β-cell hyperfunction induced by chronic hyperglycemia [14] and a direct influence of hydrogen ions [9], which leads to the development of "steroid diabetes" [5].

Special experiments on hypophysectomized animals were carried out to evaluate the role of HHAS hyperfunction in the development of insular insufficiency caused by ABB disturbances. It was found (Fig. 1, *b*) that, as in our previous studies [6], a blockade of HHAS 3 days after hypophysectomy lowers the fasting blood sugar level by 16.9%, while the glycemia level does not differ

TABLE 1. Effect of Acidosis and Alkalosis on the Content of Homones in Rat Plasma ($M \pm m$)

Experimental conditions	Hormone		
	Insulin, pmol/liter	Glucagon, pg/ml	Corticotropin, pg/ml
Control (10)	127.84±13.28	71.02±5.60	78.91±5.72
Acute administration:			
NH_4Cl (12)	191.22±20.91 $p<0.05$	106.42±23.33 $p>0.1$	118.28±12.82 $p<0.02$
$NaHCO_3$ (10)	86.59±15.84 $p<0.05$	123.16±10.48 $p<0.001$	62.00±5.32 $p<0.05$
Long-term administration:			
NH_4Cl (9)	91.18±6.98 $p<0.05$	62.17±3.81 $p>0.2$	131.18±13.84 $p>0.5$
$NaHCO_3$ (8)	67.89±8.31 $p<0.01$	116.35±5.35 $p<0.001$	169.58±37.03 $p<0.05$

Note. The number of animals is shown in parentheses.

from that in intact control rats, thus suggesting sufficient activity of the β cells of the Langerhans islets. Acidosis in hypophysectomized animals lowers the fasting glycemia level by 44.6%. The maximal glycemia level in response to the sugar load was 39% lower in these rats in comparison to the control hypophysectomized animals, while the blood sugar level 120 min after the last glucose load was close to the control value. The data suggest that under conditions of HHAS blocade long-term acidosis does not deplete the insular β cells of the pancreas.

Alkalosis in hypophysectomized rats elevates the fasting glycemia level and results in double-bell-shaped sugar curves, although the maximal glycemia level in these rats is even somewhat lower then in the controls, which implies a functional character of insulin insufficiency.

Thus, a long-term shift of the ABB in either the alkaline or acid direction can lead to the development of diabetes mellitus. The root cause of the diabetogenic influence of chronic acidosis, in our opinion, is an overproduction of glucocorticoids, resulting in a depleting stimulatory influence of glucose on the β cells, whereas alkalosis exerts a primary suppressive effect on the α-cells of the Langerhans islets.

REFERENCES

1. N. V. Krishtal', A. I. Mardar', and L. I. Sandulyak, in: *First Ukrainian Congress of Anatomists, Histologists, Embryologists, and Topographoanatomists, Abstracts*, Vinnitsa (1980), p. 109.
2. N. V. Krishtal', in: *Problems of Pathology in Experiment and Clinical Practice* [in Russian], Vol. 2, L'vov (1989), pp. 104-105.
3. N. V. Krishtal' and A. L. Kukharchuk, in: *Fourth All-Union Congress of Pathophysiologists, Abstracts*, Vol. 3, Moscow (1989), p. 1200.
4. N. V. Krishtal', in: *Functional Reserves and Adaptation* [in Russian], Kiev (1990), pp. 327-330.
5. S. M. Leites and T. S. Yakushev, *Probl. Endokrinol.*, **1**, № 6, 47-56 (1955).
6. A. I. Mardar' and N. V. Krishtal', *Fiziol. Zh.*, **27**, № 1, 60-63 (1981).
7. J. Tepperman and H. Tepperman, *Metabolic and Endocrine Physiology*, Chicago-London (1987).
8. P. Bergsten, F. Rorsman, and B. Hellman, *Acta Physiol., Scand*, **128**, № 4, 619-628 (1986).
9. L. Best, E. A. Bone, J. E. Meats, and S. Tomlinson, *Molec. Endocrinol.*, **1**, № 1, 33-38 (1988).
10. L. W. Frazier, *Proc. Soc. Exp. Biol. Med.*, **187**, № 4, 425-431 (1988).
11. J. C. Henquin, *Hormone Res.*, **27**, № 3, 168-178 (1987).
12. C. S. Pace and J. T. Tarvin, *J. Membrane Biol.*, **73**, № 1, 39-49 (1983).
13. E. Panzig, W. Besch, K.-D. Rosenbaum, *et al., Exp. Clin. Endocrinol.*, **86**, № 1, 61-68 (1985).
14. G. C. Weir, S. Bonner-Weir, and J. J. Leahy, *Diabetes: Proc. 13th Congr. Int. Diabetes Fed., Sydney, Nov. 20-25*, (1988), pp. 335-339.