0163-4984/92/3201-3—0305 $02.00

Zinc and Insulin Sensitivity

PATRICE FAURE,*[1] ANNE ROUSSEL,[1] CHARLES COUDRAY,[1] MARIE JEANNE RICHARD,[1] SERGE HALIMI,[2] AND ALAIN FAVIER[1]

[1]Laboratoire de Biochimie C, Hôpital A. Michallon, BP 217 X, F. 38043 Grenoble Cedex, France; and [2]Laboratoire de recherche métabolique Université Joseph Fourier, Domaine de la merci, F.38700 La Tronche, France

Received January 31, 1991; Accepted May 23, 1991

ABSTRACT

Many studies have shown that zinc deficiency could decrease the response to insulin. In genetically diabetic animals, a low zinc status has been observed contrary to induced diabetic animals. The zinc status of human patients depends on the type of diabetes and the age. Zinc supplementation seems to have beneficial effects on glucose homeostasis. However, the mechanism of insulin resistance secondary to zinc depletion is yet unclear. More studies are therefore necessary to document better zinc metabolism in diabetes mellitus, and the antioxidant activity of zinc on the insulin receptor and the glucose transporter.

Index Entries: Diabetes mellitus; zinc deficiency; insulin-resistance; antioxidant; insulin receptor; glucose transporter.

INTRODUCTION

Zinc is known to be an essential trace element. Since Scott, who demonstrated in 1934 that zinc forms an integral part of crystallin insulin, a number of studies on the relation between this trace element and diabetes mellitus have been performed. However, they showed conflicting results concerning zinc status. This contribution deals with zinc status and glucose metabolism during diabetes mellitus, and tries to

*Author to whom all correspondence and reprint requests should be addressed.

understand the insulin resistance mechanism observed during zinc deficiency by discriminating between hepatic and peripheral effects of zinc on insulin sensitivity.

ZINC AND METABOLIC PATHWAY RELATED TO GLUCOSE METABOLISM

In most mammalian species, insulin is stored in β cells of pancreas as zinc crystals (*1*). The addition of zinc to insulin is known to induce conformational changes and enhancement of insulin binding to its receptor (*2*). Beside this activity, the element is a constituent of many enzymes involved in glucose metabolism, either as activator (fructose 1-6 diphosphate aldolase) or as inhibitor (fructose 1-6 diphosphatase). Zinc is also an enzymatic cofactor for lipid (Δ6, Δ9 desaturase) and protein metabolisms. The modification in lipid metabolism secondary to zinc deficiency could impair glucose transporter function as shown by in vitro studies on isolated cells (*2*).

ZINC STATUS AND DIABETES MELLITUS

Tissue zinc decrease has been reported in genetically diabetic mice (Db/Db) or diabetic obese rats (ob/ob) (*3*). This is in contrast with findings in animal models of type I diabetes mellitus (Streptozotocin and alloxan induced) where tissue zinc level appears to be normal. Most of the investigations concerning zinc status in humans show a decreased serum zinc level, the degree of the depletion depending on the type of diabetes and the age of the patients (*4*). The insulin treatment leads to an increase in plasma zinc levels and zincuria. Also, most authors evidence an increased renal loss of zinc (*5*), which is independent on the type and duration of diabetes. The consequence of zinc renal loss on tissue zinc status is yet unclear, and the correlation between zincuria and tissue zinc level is not established.

ZINC AND INSULIN-SENSITIVITY TESTS IN THE ANIMALS

Zinc-deficient animals show glucose intolerance during iv glucose challenge. In order to measure separately the hepatic and the peripheral insulin-sensitivity, we determined the insulin sensitivity using the euglycemic hyperinsulinic glucose clamp technique coupled with tritiated glucose as a tracer (*6*). In this technique, a constant insulin rate is perfused and glycemia measured every 5 min. The glucose infusion rate is adapted to reach a steady state. Tritiated glucose is used to measure hepatic insulin sensitivity by measuring the decrease in hepatic glucose

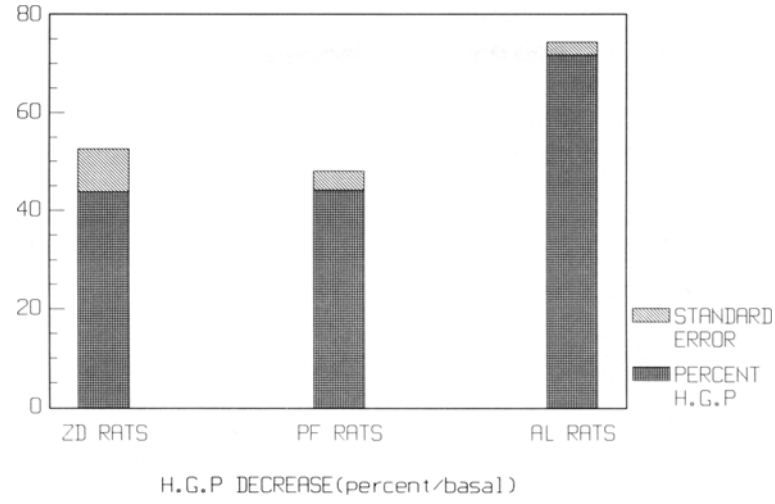

Fig. 1. Percentage of hepatic glucose production decrease during insulin perfusion (at 0.6 mU/min).

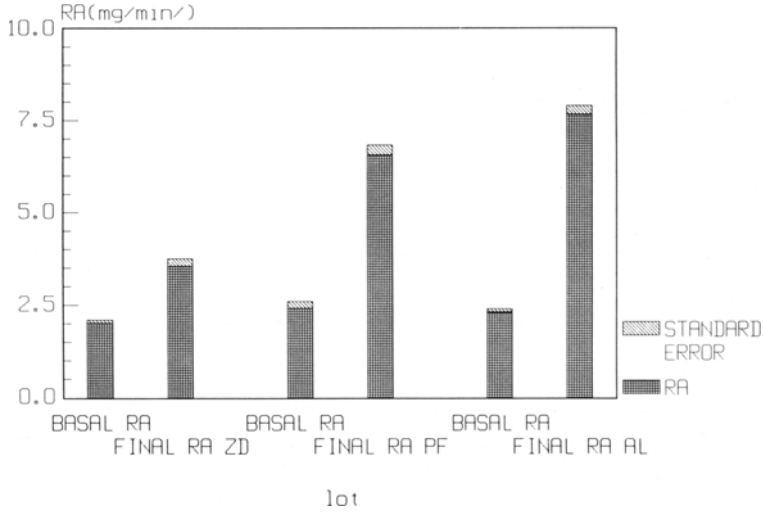

Fig. 2. Basal and final glucose turnover (RA) after 1 h of insulin infusion (at 9 mU/min/rat).

production. At the steady state, the glucose infusion rate equals the glucose captation and reflects insulin sensitivity. At 0.6 mU/min/rat of insulin infusion rate, we did not evidence a decreased hepatic insulin sensitivity in zinc-deficient rats compared to pair-fed rats (Fig. 1). At 9 mUI/min/rat, the zinc-deficient rats show a peripheral insulin resistance (Fig. 2). In this case, the insulin resistance could be secondary to post-receptor events as previously described (7).

ZINC SUPPLEMENTATION OF DIABETIC PATIENTS

At the moment, there are few studies concerning the effects of zinc supplementation in diabetic patients. Winterberg et al. supplemented with zinc (50 mg/d) type I (n = 24) and type II (n = 25) diabetic patients, and observed after 20 d a significant decrease in glycemia and cholesterolemia (*8*). More studies with a longer treatment period are necessary to confirm these results, but they are difficult to perform because of the need for long supplementation periods (more than 3 mo) and the eventual changes in glucose homeostasis independently on zinc supplementation (intercurrent disease, infections, and so on).

Because of the various effects of zinc supplementation on zinc status in diabetic patients, it seems relevant to perform zinc absorption studies with stable isotopic tracers to compare zinc absorption in diabetic patients and controls, in order to determine whether the type and the evolution of diabetes mellitus could affect the zinc absorption. Such studies will constitute a valuable contribution to the understanding of zinc status during diabetes mellitus.

MECHANISM OF INSULIN RESISTANCE DURING ZINC DEFICIENCY

During oral glucose tolerance tests, Hendricks and Mahoney (*9*) did not observe glucose intolerance in zinc-deficient rats when compared to controls. This is in contrast with iv glucose tolerance tests, where Huber and Gershoff reported a glucose intolerance (*10*). This impaired glucose clearance was confirmed in force-fed zinc-deficient rats (*11*), which is a model to discriminate between a direct role of zinc and the decreased appetite induced by zinc deficiency.

The effect of zinc deficiency on insulin secretion by the pancreas could be one of the mechanisms of glucose intolerance (*12*). Nevertheless, some authors found minor impairment in insulin secretion during zinc-deficient diets. Zinc also plays a role in insulin behavior since it can enhance the insulin binding to hepatocyte membranes (*13*). In our studies, with isolated adipocytes, we did not find an impaired insulin binding in zinc-deficient rats and pair-fed rats (Fig. 3), suggesting that the caloric restriction secondary to zinc deficiency has a role in insulin resistance as confirmed by in vivo studies. The insulin binding is not different when tested at 37°C, where intracellular and surface receptors are involved, and at 16°C, where the receptor translocation is inhibited leading only to insulin binding at surface receptors.

The importance of zinc on insulin receptor synthesis is an additional way to explain the decreased hepatic insulin binding during zinc defi-

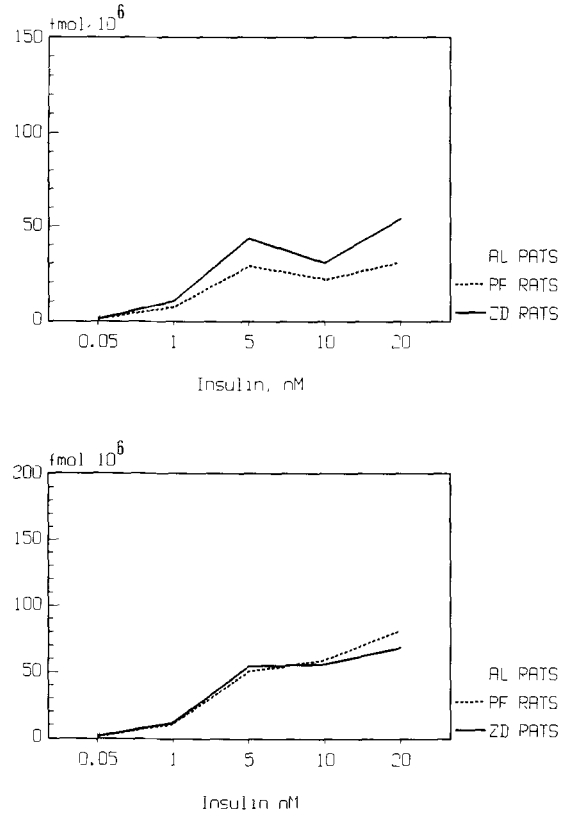

Fig. 3. Insulin binding to rat adipocytes at 37°C and 16°C.

ciency (*14*). The effect of zinc deficiency on peripheral glucose metabolism could be related to the action of zinc on glucose transporter translocation inside the cells or by the modification of glucose transporter structure (*15*). The latest mechanism takes into account the role of zinc as a biological antioxidant. Some studies showed that lipid peroxidation is increased during diabetes mellitus (*16*) and that superoxide dismutase (SOD) shows low activity (*17,18*). This increased peroxidation could affect insulin or glucose transporter function by having a direct effect on proteins or by having an indirect effect on membrane fluidity, such as previously described (*19*). It is known that zinc takes part in the structure of SOD and is necessary for optimum enzyme activity (*20*). Zinc also increases synthesis of metallothionein, which is a free radical scavenger. The supplementation of pancreatic culture medium with zinc increases insulin secretion and prevents peroxide formation with Alloxan® (*21*). More human studies are, however, necessary to document the activity of zinc better as a biological antioxidant in diabetic patients, and make the correlation between lipid peroxidation and insulin-receptor function.

REFERENCES

1. Y. A. A. Lazaris and Z. E. Bavel'skii, *Bull. Exp. Biol. Med.* **77,** 647 (1980).
2. E. R. Arquilla, S. Paker, W. Tarmas, and S. Miyamoto, *Endocrinology* **103,** 1440 (1978).
3. A. S. E. Levine, C. J. Mc Clain, B. S. Handwerger, D. M. Brown, and J. E. Morley, *Am. J. Clin. Nutr.* **37,** 382 (1983).
4. A. D. M. Oorodian and A. D. Morley, *Am. J. Clin. Nutr.* **45,** 877 (1987).
5. W. B. Kinlaw, A. S. Levine, J. E. Morley, S. E. Silvis, and C. J. Mc Clain, *Am. J. Medicine* **75,** 273 (1982).
6. P. Faure, A. M. Roussel, M. Osman, A. Favier, and S. Halimi, *Diab. Met.* in press (1991).
7. S. Halimi, F. Assimacopoulos, J. Terretaz, and B. Jeanrenaud, *Diabetologia* **80,** 268 (1987).
8. B. Winterberg, M. Bochichio, T. H. Hossdonf, H. Lahl, A. E. Lison, and H. Zumkley, *Trace El. Med.* **6,** 173 (1989).
9. D. G. Hendricks and A. W. Mahoney, *Nut. Food Sciences* **102,** 1079 (1972).
10. A. M. Huber, and S. Gershoff, *J. Nutr.* **103,** 1739 (1973).
11. J. H. Y. Park, J. Carter, M. H. Hart, S. U. Endman, P. Pour, and J. A. Vanderhoof, *Am. Phys. Soc.* **251,** 273 (1986).
12. S. L. Howell, M. Tyhurst, H. Dubefelt, A. Anderson, and C. Hellstorm, *Cell. Tiss. Res.* **107,** 118 (1978).
13. A. C. Herington, *Horm. Metab. Res.* **11,** 853 (1985).
14. H. Y. Jung, G. J. Carter, and M. D. Vanderhoof, *Nut. Res.* **9,** 183 (1989).
15. T. J. Wheeler and P. C. Hinckle, *Am. J. Phys.* **47,** 503 (1985).
16. S. K. Jaim, R. Mc Vie, J. Duett, and J. Herbst, *Diabetes,* **38,** 1539 (1989).
17. D. V. Godim, S. A. Wahaieb, M. E. Garnett, and A. D. Goumeniouk, *Biochemistry* **84,** 223 (1988).
18. N. Nath, S. N. Chari, and A. B. Rath, *Diabetes* **33,** 586 (1984).
19. A. M. Michelson, K. Puget, and P. Durosay, *C. R. Soc. Biol.* **179,** 429 (1985).
20. C. Coudray, M. J. Richard, F. Laporte, A. M. Roussel, and A. Favier, *Clin. Chem. J.* in press (1991).
21. J. M. May and S. Contoreggi, *J. Biol. Chem.* **257,** 4362 (1981).