Oxidative Stress and Glycemic Regulation

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Oxidative stress is an acknowledged pathogenetic mechanism in diabetic complications. Hyperglycemia is a widely known cause of enhanced free radical concentration, whereas oxidative stress involvement in glycemic regulation is still debated. Glucose transport is a cascade of events starting from the interaction of insulin with its own receptor at the plasma membrane and ending with intracellular glucose metabolism. In this complex series of events, each step plays an important role and can be inhibited by a negative effect of oxidative stress. Several studies show that an acute increase in the blood glucose level may impair the physiological homeostasis of many systems in living organisms. The mechanisms through which acute hyperglycemia exerts these effects may be identified in the production of free radicals. It has been suggested that insulin resistance may be accompanied by intracellular production of free radicals. In adipocytes cultured in vitro, insulin increases the production of hydrogen peroxide, which has been shown to mimic the action of insulin. These data allow us to hypothesize that a vicious circle between hyperinsulinemia and free radicals could be operating: insulin resistance might cause elevated plasma free radical concentrations, which, in turn, might be responsible for a deterioration of insulin action, with hyperglycemia being a contributory factor. Data supporting this hypothesis are available. Vitamin E improves insulin action in healthy, elderly, and non-insulin-dependent diabetic subjects. Similar results can be obtained by vitamin C administration.

OXIDATIVE DAMAGE INFLICTED by reactive oxygen species is referred to as "oxidative stress."[1] In diabetes, oxidative stress seems mainly caused by both an increased production of plasma free radical concentrations and a sharp reduction in antioxidant defenses.[2] Among the causes of enhanced free radical production, hyperglycemia,[3] hyperinsulinemia,[4] and/or insulin resistance[5] seem to play a major role.

Although the relationship between oxidative stress and diabetic complications has been extensively investigated, the possible role of oxidative stress in glycemic regulation is still a neglected area. However, there is evidence that enhanced plasma free radical concentrations may impair insulin action, thus contributing to the generation of hyperglycemia, while hyperglycemia and insulin resistance, by themselves, may produce oxidative stress.

Hyperglycemia and Oxidative Stress

Hyperglycemia is a widely known cause of enhanced plasma free radical concentrations.[3] Free radical production caused by hyperglycemia may occur via at least 3 different routes: nonenzymatic glycation,[6] auto-oxidation of glucose,[7] and intracellular activation of the polyol pathway.[8] Published studies show that an acute increase in blood glucose concentration can impair physiological homeostasis in various systems in the living organism and that antioxidants can oppose these effects.[3] These results provide indirect evidence that hyperglycemia induces an oxidative stress. More direct evidence comes from studies on total radical-trapping antioxidant parameter (TRAP). Extracellular fluids lack protection by antioxidant enzymes, but contain several molecules that delay or inhibit the oxidative process.[9] The majority of these molecules have multiple antioxidant properties, so that the total antioxidant capacity of the plasma is determined not only by the concentration of individual antioxidants but also by their synergy.[9] An assay of TRAP has been proposed recently to evaluate plasma antioxidant capacity, a measure of the concentration of antioxidants and their mutual cooperation. Reduced TRAP activity has been reported in patients with type 1 or type 2 diabetes.[10,11]

The impact of hyperglycemia on antioxidant status in diabetic and nondiabetic subjects has recently been evaluated. During an oral glucose tolerance test, the plasma concentrations of protein-bound sulfydryl groups, vitamin C, and uric acid, as well as TRAP, decreased significantly.[12] These results were similar in both healthy individuals and patients with type 2 diabetes.[12] This finding confirms that hyperglycemia provokes oxidative stress, which leads to depletion of antioxidant capacity.

Insulin Resistance and Oxidative Stress

Findings in animal models indicate that rats with insulin resistance show signs of increased lipid peroxidation.[13] In adipocytes cultured in vitro, insulin increases the production of H_2O_2,[14] which has been shown to mimic the action of insulin.[15] Furthermore, the administration of vanadium reproduces the action of insulin[16] through the intercellular release of free radicals.[17] This is consistent with the observation that hyperinsulinemia, in vivo, decreases vitamin E concentrations, suggesting that increased levels of insulin may produce an oxidative stress.[18] These findings convincingly support the hypothesis that insulin resistance is linked to the presence of an oxidative stress.[5]

Effects of Oxidative Stress on Insulin Action

Increased oxygen radical production associated with a reduction in plasma antioxidants, particularly glutathione, may have toxic effects on the plasma membrane structure/activity of the β cells, contributing to the impaired insulin secretion in diabetes.[4] In fact, in vitro studies showed that membrane-penetrating thiol oxidants impair insulin secretion, whereas an increase in extracellular glutathione or cysteine enhances the β-cell response to glucose.[19,20] Moreover, it seems plausible that oxidative stress also reduces insulin action, because in the β cells, which are more susceptible to the effects of free radicals than other tissues,[21] it produces a consistent decrease in the expres-

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sion of glucose transporters.[22] These data are in accord with the in vivo evidence that in diabetic patients both the concentration of free radicals and the levels of glutathione condition insulin action.[23,24] Moreover, the role of oxidative stress in worsening insulin action is evidenced by studies with antioxidants. In fact, in insulin-resistant rats, vitamin E increases insulin sensitivity,[25] whereas vitamin C and vitamin E are not only able to restore insulin action in type 2 diabetic patients but also improve insulin secretion in normal subjects.[26,27]

CONCLUSION

The previously discussed evidence supports the hypothesis that oxidative stress may be involved in glycemic regulation in diabetes. Both hyperglycemia and insulin resistance are accompanied by reduced insulin action.[28] However, hyperglycemia and insulin resistance, typical features of type 2 diabetes, may be accompanied by oxidative stress,[3,5] which, in itself, may produce decreased insulin secretion/action.[4] Therefore, it may be hypothesized that oxidative stress represents the common pathway through which hyperglycemia and insulin resistance induce depressed insulin action (Fig 1). This point of view is supported by studies with antioxidants, which are able to improve insulin action.[26,27] Moreover, from this evidence, it can also be hypothesized that during a meal, a period characterized by a simultaneous increase in glycemia, derangement of insulin resistance, and increased requirement of insulin action, there should be an increased oxidative stress generation. This hypothesis has been recently confirmed in type 2 diabetic patients.[29] From a clinical point of view, this means that a meal may be the ideal time for antioxidant supplementation in diabetes.

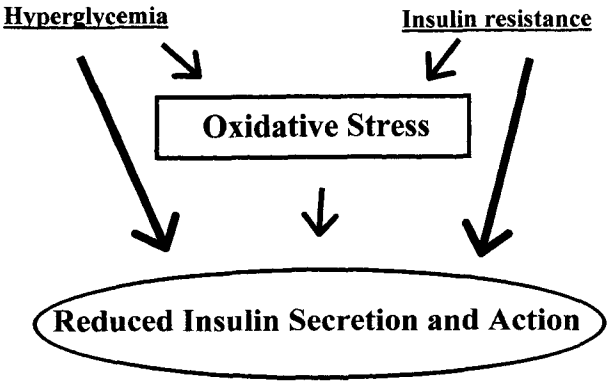

Fig 1. Hyperglycemia and insulin resistance are accompanied by reduced insulin action. However, both are also linked to the generation of an oxidative stress, which can also produce, in itself, an impaired insulin action. It can be hypothesized that the oxidative stress represents the common pathway through which hyperglycemia and insulin induce a depressed insulin action.

REFERENCES

1. Cross CE, Halliwell B, Borish ET, et al: Oxygen radicals and human disease. Ann Intern Med 107:526-545, 1987

2. Giugliano D, Ceriello A, Paolisso G: Oxidative stress and diabetic vascular complications. Diabetes Care 19:257-267, 1996

3. Ceriello A: Acute hyperglycaemia and oxidative stress generation. Diabet Med 14:S45-S49, 1997 (suppl 1)

4. Paolisso G, Guigliano D: Oxidative stress and insulin action: Is there a relationship? Diabetologia 39:357-363, 1996

5. Ceriello A, Pirisi M: Is oxidative stress the missing link between insulin resistance and atherosclerosis? Diabetologia 38:1484-1485, 1995

6. Ceriello A, Quatraro A, Giugliano D: New insights on non-enzymatic glycosylation may lead to therapeutic approaches for the prevention of diabetic complications. Diabet Med 9:297-299, 1992

7. Wolff SP, Dean RT: Glucose auto-oxidation and protein modification. The potential role of "autoxidative glycosylation" in diabetes. Biochem J 245:243-250, 1987

8. Williamson JR, Chang K, Frangos M, et al: Hyperglycemic pseudohypoxia and diabetic complications. Diabetes 42:801-813, 1993

9. Halliwell B, Gutteridge JMC: The antioxidants of human extracellular fluids. Arch Biochem Biophys 280:1-8, 1990

10. Tsai EC, Hirsch IB, Brunzell JD, et al: Lower plasma peroxyl radical trapping capacity and higher susceptibility of LDL to oxidation in poorly controlled IDDM. Diabetes 43:1010-1014, 1994

11. Ceriello A, Bortolotti N, Falleti E, et al: Total radical-trapping antioxidant parameter in non-insulin-dependent diabetic patients. Diabetes Care 20:194-197, 1997

12. Ceriello A, Bortolotti N, Crescentini A, et al: Antioxidant defences are reduced during the oral glucose tolerance test in normal and non-insulin-dependent diabetic subjects. Eur J Clin Invest 28:329-333, 1998

13. Kazdovà L, Vràna A, Matejckovà M, et al: Increased lipid peroxidation in an experimental model of metabolic syndrome X: Effect of dietary oils. Diabetologia 37:533, 1994 (abstr, suppl 1)

14. Muchmore DB, Little SA, deHaen C: Counterregulatory control of intracellular hydrogen peroxide production by insulin and lipolytic hormones in isolated rat epididymal fat cells: A role for free fatty acids. Biochemistry 21:3886-3892, 1982

15. Hayes GR, Lockwood DH: Role of insulin receptor phosphorylation in the insulinomimetic effects of hydrogen peroxide. Proc Natl Acad Sci USA 84:8115-8119, 1987

16. Heffetz D, Bushkin J, Dror R, et al: The insulinomimetic agent H_2O_2 and vanadate stimulate protein tyrosine phosphorylation in intact cells. J Biol Chem 265:2896-2902, 1990

17. Yin X, Davison AJ, Tsang SS: Vanadate-induced gene expression in mouse C127 cells: Roles of oxygen derived active species. Mol Cell Biochem 115:85-96, 1992

18. Galvan AQ, Muscelli E, Catalano C, et al: Insulin decreases circulating vitamin E levels in humans. Metabolism 45:998-1003, 1996

19. Ammon HPT, Grimm A, Lutz S, et al: Islet glutathione and insulin release. Diabetes 29:830-834, 1980

20. Ammon HPT, Hehl TK, Enz G, et al: Cysteine analogues potentiate glucose-induced insulin secretion in vitro. Diabetes 35:1390-1396, 1986

21. Tiedge M, Lortz S, Drinkgern J, et al: Relation between antioxidant gene expression and antioxidative defense status of insulin-producing cells. Diabetes 46:1733-1742, 1997

22. Rudich A, Korlovsky N, Potashnik R, et al: Oxidant stress reduces insulin responsiveness in 3T3-L1 adipocytes. Am J Physiol 272:E935-E940, 1997

23. Paolisso G, Di Maro G, Pizza G, et al: Plasma GSH/GSSG affects glucose homeostasis in healthy subjects and non-insulin-dependent diabetics. Am J Physiol 263:E435-E440, 1992

24. Paolisso G, D'Amore A, Volpe C, et al: Evidence for a relationship between oxidative stress and insulin action in non-insulin-dependent (type II) diabetic patients. Metabolism 43:1426-1429, 1994

25. Faure P, Rossini E, Lafond JL, et al: Vitamin E improves the free radical defense system potential and insulin-sensitivity of rats fed with high fructose diets. J Nutr 123:103-107, 1997

26. Paolisso G, D'Amore A, Balbi V, et al: Plasma vitamin C affects glucose homeostasis in healthy subjects and non-insulin-dependent diabetics. Am J Physiol 266:E261-E268, 1994

27. Paolisso G, D'Amore A, Giugliano D, et al: Pharmacological doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients. Am J Clin Nutr 57:650-656, 1993

28. De Fronzo RA, Bonnadonna RC, Ferrannini E: Pathogenesis of NIDDM: A balanced overview. Diabetes Care 15:318-368, 1992

29. Ceriello A, Bortolotti N, Motz E, et al: Meal-generated oxidative stress in type 2 diabetic patients. Diabetes Care 21:1529-1533, 1998