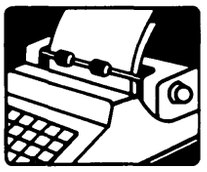
# Editorial



## Current Status of Aldose Reductase Inhibitors

The search for ways to prevent or treat the chronic complications of diabetes absorbs the efforts of many researchers whose work is presented in *Diabetes Care*. That search has concentrated on identification of the relationship between hyperglycemia and complications and on the development of treatment to prevent the metabolic alterations induced by hyperglycemia. Recently, aldose reductase inhibitors have received much attention, including at least two published symposia (1,2) and favorable comment in the *Wall Street Journal*. Surprisingly, *Diabetes Care* has published very little on aldose reductase inhibitors. Although several reviews are available (3–5), and data analysis in our own studies is under way, we thought a commentary on their current status was warranted.

These agents represent an example of the interactions among basic research, pharmaceutical industry, and clinical trials. The sorbitol pathway was first identified in seminal vesicles in 1956 and became linked to diabetes when sorbitol accumulation was noted in the cataracts of rats with diabetes in 1959 (6). Since then, the enzyme aldose reductase has been found in the pericytes of retinal capillaries, Schwann cells of the myelin sheath, and renal glomeruli in addition to other cells less directly involved in diabetic complications.

Glucose utilization for glycolysis usually proceeds through phosphorylation to glucose 6-phosphate by hexokinase but may alternatively occur after conversion of glucose to fructose through the sorbitol or polyol pathway. In this pathway the rate-limiting enzyme aldose reductase converts glucose to sorbitol, which is then converted to fructose by sorbitol dehydrogenase. At least in some tissues, elevated glucose saturates hexokinase and activates aldose reductase, leading to increased flux through the pathway. Aldose reductase has broad substrate specificity reducing several aldehydes, e.g., galactose, xylose, and arabinose. Galactose is converted to dulcitol, and in animal experiments a high-galactose diet produces changes in the eyes and kidneys similar to those seen in diabetes.

In the lens of the eye, sugar alcohols can accumulate in sufficient concentration to produce a hyperosmotic effect and cellular pathology (4). Because of lower enzyme concentration and sugar alcohol accumulation, it is less certain that the osmotic hypothesis applies to other tissues. Some evidence suggests that increased sorbitol pathway activity reduces nerve *myo*-inositol content, altering nerve phosphoinositide metabolism and impairing $Na^+$-$K^+$-ATPase activity (7). Other studies indirectly connect the sorbitol pathway and basement membrane thickening (8,9).

The link between the sorbitol pathway and diabetic complications has been strengthened by studies with aldose reductase inhibitors. In the 1960s, long-chain fatty acids were shown to inhibit aldose reductase in lens homogenates. Next, tetramethylene glutaric acid was shown to block dulcitol synthesis in lenses incubated in a high-galactose medium. Alrestatin was the first inhibitor to be used effectively in vivo. Subsequently, studies have identified a common molecular structure and schematic inhibitor site for inhibitors, which has resulted in the synthesis of many inhibitors (10). The potential benefit (and potential profit) from these medications has created a competitive environment with many animal and human trials. Currently, the most promising of the inhibitors are Sorbinil, Tolrestat, ONO 2235, and Statil.

Many studies in diabetic and galactosemic experimental animals have conclusively established that aldose reductase inhibitors can prevent cataracts (11,12), diminish urinary protein excretion (13), and correct slowing of nerve conduction (14–17). Unfortunately, the results of clinical trials in humans with diabetes have been much less convincing (18–25). These have all examined neuropathy, and, although subjective symptoms of pain may improve, objective measurements either show no improvement or only show slight improvement of unknown clinical significance. This stresses some of the major problems in studies of neuropathy. Measures of symptoms are generally poorly standardized, and response is highly subject to placebo effects. More objective measures, such as electrophysiologic studies, are subject to considerable variability. This raises questions regarding the clinical significance of minimal electrophysiological changes and creates great difficulty in multicenter trials.

In addition, most trials have been short. It may take a much longer treatment course to measure any improvement

or prevention of progression. This is a particular problem in the subjects with severe neuropathy who have been examined in most studies.

Several other factors temper enthusiasm for these agents. Animal experiments suggest aldose reductase inhibitors are most effective when used to prevent early changes and, at least in galactasemic cataracts, are ineffective once the cataract has advanced past a certain point (26). Thus, aldose reductase inhibitors will probably need to be taken by the patient for many years. Therefore, drug toxicity becomes a major concern. Sorbinil, the most widely tested aldose reductase inhibitor, has been associated with at least a 10% incidence of severe reversible hypersensitivity reactions during the first 2 mo of administration at a dose of 250 mg daily. Lower doses may avoid this problem, but the side-effect incidence may be unacceptably high in a drug used for prevention. Preliminary information suggests Tolrestat may be safer, but the long-term safety of all these drugs is unknown. Compounding this concern is the poorly understood physiologic role of aldose reductase. Might there be an unexpected disadvantage to inhibiting this enzyme? Aldose reductase is a heterogeneous enzyme with various functions and some differences from tissue to tissue (27). Because effective inhibition is achieved in one tissue or animal, it cannot be assumed to extend to all tissues. Conversely, whereas inhibition may be advantageous in one tissue, it may be disadvantageous in another.

Although the sorbitol pathway is firmly established as one mechanism by which hyperglycemia alters cellular metabolism, it is unlikely to represent the only meaningful metabolic alteration leading to adverse effects. Although links between sorbitol accumulation, membrane function, and basement membrane thickening have been tentatively established, they are not understood completely (28). Sugar alcohols do not participate in glycosylation of proteins, leaving this important developing area of understanding of diabetic complications seemingly unrelated to the sorbitol pathway. No link has even been suggested between the sorbitol pathway and the immunoglobulin trapping recently reported to be present on the nerve myelin from patients with diabetes (29). The finding that an aldose reductase inhibitor could prevent sorbitol accumulation in the sciatic nerves of diabetic rats but did not reverse the retardation of some aspects of axonal transport also suggests a heterogeneous etiology for these defects (30). Thus, even if effective, the aldose reductase inhibitors may only ameliorate but not eliminate the chronic complications of diabetes.

The reported studies can be viewed from two perspectives. The progression of our knowledge of the sorbitol pathway and its relationship to the complications of diabetes from basic research, to the development of inhibitors, and to potential clinical application represents medical science at its best. It also demonstrates the benefit of cooperation between basic scientists, clinicians, and the pharmaceutical industry. On the other hand, the clinical trials have demonstrated serious gaps in our methods and have generally been disappointing. Obviously, we must advance on two fronts. Basic investigations into the pathophysiologic mechanisms must continue. Equally important are more sophisticated clinical trials. These should be designed to study alterations in many tissues with the most accurate measuring techniques available, to search for subtle adverse effects of the drugs, to last long enough to make reasonable judgments, and perhaps to identify which subgroups of patients benefit most from treatment.

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REFERENCES


1. Proceedings: Diabetic complications and the role of aldose reductase inhibition. *Am J Med* 79:Suppl. 5A, 1985
2. Proceedings: The effects of Sorbinil on the pathophysiology of diabetic complications. *Metabolism* 35:Suppl. 1, 1986
3. Kinoshita JH, Kador PF, Robison G, Datilis MB, Cobo LM, Kupfer C: Aldose reductase and complications of diabetes. *Ann Intern Med* 101:82–91, 1984
4. Kador PF, Robison WG Jr, Kinoshita JH: The pharmacology of aldose reductase inhibitors. *Annu Rev Pharmacol Toxicol* 25:691–714, 1985
5. Greene DA, Lattimer S, Ulbrecht J, Carroll P: Glucose-induced alterations in nerve metabolism: current perspective on the pathogenesis of diabetic neuropathy and future directions for research and therapy. *Diabetes Care* 8:290–99, 1985
6. Van Heyningen R: Formation of polyols by the lens of the rat with "sugar" cataract. *Nature* (Lond) 184:195–96, 1959
7. Greene DA, Lattimer SA: Action of Sorbinil in diabetic peripheral nerve: relationship of polyol (sorbitol) pathway inhibition to a *myo*-inositol–mediated defect in sodium-potassium ATPase activity. *Diabetes* 33:712–16, 1984
8. Frank RN, Keirn RJ, Kennedy A, Frank KW: Galactose-induced retinal capillary basement membrane thickening: prevention by Sorbinil. *Invest Ophthalmol Visual Sci* 24:1519–24, 1983
9. Robison WG Jr, Kador PF, Kinoshita JH: Retinal capillaries: basement membrane thickening by galactosemia prevented with aldose reductase inhibitor. *Science* 22:1177–79, 1983
10. Kador PF, Sharpless NE: Pharmacophor requirements of the aldose reductase inhibitor site. *Mol Pharmacol* 24:521–31, 1983
11. Gonzalez AM, Sochor M, McLean P: The effect of an aldose reductase inhibitor (Sorbinil) on the level of metabolites in lenses of diabetic rats. *Diabetes* 32:482–85, 1983
12. Beyer-Mears A, Cruz E: Reversal of diabetic cataract by Sorbinil, an aldose reductase inhibitor. *Diabetes* 34:15–21, 1985
13. Beyer-Mears A: The polyol pathway, Sorbinil, and renal dysfunction. *Metabolism* 51:46–54, 1986
14. Tomlinson DR, Holmes PR, Mayer IH: Reversal, by treatment with an aldose reductase inhibitor, of impaired axonal transport and motor nerve conduction velocity in experimental diabetes mellitus. *Neurosci Lett* 31:189–93, 1982
15. Yue DK, Hanwell MA, Satchell PM, Turtle JR: The effect of aldose reductase inhibition on motor nerve conduction velocity in diabetic rats. *Diabetes* 31:789–94, 1982
16. Mayer JH, Tomlinson DR: Prevention of defects of axonal transport and nerve conduction velocity by oral administration of *myo*-inositol or an aldose reductase inhibitor in streptozotocin-diabetic rats. *Diabetologia* 25:433–38, 1983

17. Kikkawa R, Hatanaka I, Yasuda H, Kobayashi N, Shigeta Y: Prevention of peripheral nerve dysfunction by an aldose reductase inhibitor in streptozotocin-diabetic rats. *Metabolism* 33:212–15, 1984
18. Fagius J, Jameson S: Effects of aldose reductase inhibitor treatment in diabetic polyneuropathy—a clinical and neurophysiological study. *J Neurol Neurosurg Psychiatry* 44:991–1001, 1981
19. Handelsman DJ, Turtle JR: Clinical trials of an aldose reductase inhibitor in diabetic neuropathy. *Diabetes* 30:459–64, 1981
20. Judzewitsch RG, Jaspan JB, Polovsky KS, Weinberg CR, Halter JB, Halar E, Pfeifer MA, Uukadinovic C, Bernstein L, Schneider M, Liang KY, Gabbay KH, Rubenstein AH, Porte D Jr: Aldose reductase inhibition improves nerve conduction velocity in diabetic patients. *N Engl J Med* 308:119–25, 1983
21. Jaspan J, Moselli R, Herold K, Bartkus C: Treatment of severely painful diabetic neuropathy with an aldose reductase inhibitor: relief of pain and improved somatic and autonomic nerve function. *Lancet* 2:758–62, 1983
22. Young RJ, Ewing DJ, Clarke BF: A controlled trial of Sorbinil, an aldose reductase inhibitor, in chronic painful diabetic neuropathy. *Diabetes* 32:938–42, 1983
23. Lewin IG, O'Brien IAD, Morgan MH, Corrall RJM: Clinical and neurophysiological studies with the aldose reductase inhibitor, Sorbinil, in symptomatic diabetic neuropathy. *Diabetologia* 26:445–48, 1984
24. Fagius J, Brattberg A, Jameson S, Berne C: Limited benefit of treatment of diabetic polyneuropathy with an aldose reductase inhibitor: a 24-week controlled trial. *Diabetologia* 28:323–29, 1985
25. Christensen JEJ, Vornek L, Gregersen G: The effect of an aldose reductase inhibitor (Sorbinil) on diabetic neuropathy and neural function of the retina: a double-blind study. *Acta Neurol Scand* 71:164–67, 1985
26. Hu TS, Datiles M, Kinoshita JH: Reversal of galactose cataract with Sorbinil in rats. *Invest Ophthalmol Visual Sci* 24:640–44, 1983
27. Terashina H, Hama K, Yamamoto R, Tsuboshima M, Kikkawa R, Hatanaka I, Shigeta Y: Effects of a new aldose reductase inhibitor on various tissues in vitro. *J Pharmacol Exp Ther* 229:226–30, 1984
28. Greene DA, Mockway AM: Decreased *myo*-inositol content and $Na^+$-$K^+$-ATPase activity in superior cervical ganglion of STZ-diabetic rat and prevention by aldose reductase inhibition. *Diabetes* 35:1106–108, 1986
29. Brownlee M, Vlassara H, Cerami A: Trapped immunoglobulins on peripheral nerve myelin from patients with diabetes mellitus. *Diabetes* 35:999–1003, 1986
30. Tomlinson DR, Sidenius P, Larsen JR: Slow component of axonal transport, nerve *myo*-inositol, and aldose reductase inhibition in streptozocin-diabetic rats. *Diabetes* 35:398–402, 1986