THE DCCT, METABOLISM AND DIABETIC NEUROPATHY: PERSPECTIVES FOR THE FOURTH INTERNATIONAL SYMPOSIUM ON DIABETIC NEUROPATHY

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From Marchal de Calvi's early recognition that diabetes caused rather than resulted from its neurologic concomitants (1), the specific role of hyperglycemia in the cause and clinical course of diabetic neuropathy remained a hotly debated issue (2) for over 100 years. The Diabetes Control and Complications Trial (DCCT) (3) unequivocally established the over-riding importance of metabolic factors associated with insulin deficiency in the pathogenesis of clinically evident, objectively confirmed diabetic polyneuropathy in subjects with insulin-dependent diabetes mellitus. Metabolic abnormalities, present in moderately controlled Type I diabetic patients and correctable by intensive metabolic therapy thus condition the pathogenesis of diabetic neuropathy (3). Hyperglycemia, as measured by HbA1c, is a reasonable metabolic candidate given the curvilinear relationship between glycemic exposure and the development and progression of diabetic complications in the DCCT (4). (Insulin deficiency per se is less likely to explain the effects of intensive vs. conventional therapy, since the total insulin dose did not differ significantly between the two DCCT treatment groups (5).) Moreover, despite substantial differences in circulating insulin levels between Type I and Type II diabetes, the risk for neuropathy and its clinical characteristics appear to be similar (6-10). Given that diabetic neuropathy also occurs in secondary forms of diabetes (pancreatectomy, nonalcoholic pancreatitis, and hemachromatosis) (11), the risk of diabetic neuropathy would appear to be independent of the underlying pathogenetic mechanisms responsible for diabetes, and of the absolute degree of insulin deficiency, but rather would appear to be a function of the diabetic state itself. Hyperglycemia, present in all forms of diabetes, therefore emerges as an attractive candidate for a common essential component to the pathogenesis of diabetic neuropathy. Duration of diabetes and attained age consistently emerge as important risk factors for diabetic neuropathy (6-10), whereas HbA1c emerges in some (8,10) but not all (6) cross-sectional studies, perhaps due to fluctuation in this measure over time. Thus, neuropathy increases with duration and perhaps severity of hyperglycemia.

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The mechanism(s) by which glucose, a vital metabolic fuel for the nervous system, at concentrations between 155 and 230 mg/dL, might confer a 3-fold increase in the risk of developing peripheral neuropathy (3) continue to pose a perplexing challenge to medical biochemists (12). Although abundant data from laboratory models suggest a wide-range of glucose-associated biochemical, functional and structural abnormalities in peripheral nerve and supporting tissue (13-16), evidence from diabetic patients for a glucose-related mechanism of peripheral nerve damage is extremely limited, consisting primarily of clinical trials with aldose reductase inhibitors. These compounds inhibit the enzyme that in human and animal peripheral nerve converts glucose to sorbitol by a NADPH-linked reaction as a function of intracellular glucose content (with subsequent oxidation of sorbitol to fructose by sorbitol dehydrogenase) (17). Potent aldose reductase inhibitors that penetrate human sural nerve and provide high-degree blockade of sorbitol formation have been shown to improve nerve conduction velocity in patients with diabetic neuropathy to an extent similar to that of intensive insulin therapy in the DCCT (18). Standardized and validated morphometric techniques (19) have demonstrated that potent aldose reductase inhibitors can reverse the progressive loss of myelinated nerve fibers in sural nerve biopsies (18) to an extent judged to be clinically meaningful based on comparison with the clinical manifestations of diabetic polyneuropathy (20). Studies in animals provide some suggestion that activation of the aldose reductase pathway may contribute to peripheral nerve damage by several of the metabolic pathways implicated in nerve damage in diabetic animals (13,15) involving shifts in cytoplasmic and mitochondrial redox couples and osmolyte depletion (Figure 1) These may lead to oxidative stress (21) and signal transduction deficits involving nitric oxide (22,23), cyclic AMP (24) and prostenoids (25), redistribution of nerve blood flow and ischemia (13,15), accelerated non-enzymatic glycation (via fructose) (26), and impaired neurotrophism. Interaction of these glucose-dependent, aldose reductase-related metabolic pathways with glucose-independent but insulin-sensitive metabolic abnormalities involving defective fatty acid metabolism and deficiency of γ–linolenic acid (15,27) may also have an important pathogenetic role. These mechanisms thus provide a conceptual basis to explain chronic neurotoxic effects of insulin deficiency and hyperglycemia that may link metabolic control to the development and progression of diabetic neuropathy.

The goal of this symposium is to provide a wide-ranging review of the mechanisms linking hypergycemia and other metabolic abnormalities associated with insulin deficiency to the development and progression of diabetic neuropathy, and to explore the clinical consequences of that interaction, based on the most current basic and clinical scientific knowledge available. For this purpose, speakers expert in many disciplines outside of the specific field of diabetic neuropathy

have been invited to share their expert knowledge with investigators devoted to understanding the pathogenesis and treatment of diabetic neuropathy. It is hoped that this intense multi-disciplinary scientific interaction will serve to catalyze new insights and new directions of scientific and clinical investigation that will ultimately benefit the millions of patients suffering from the ravages of diabetic neuropathy.

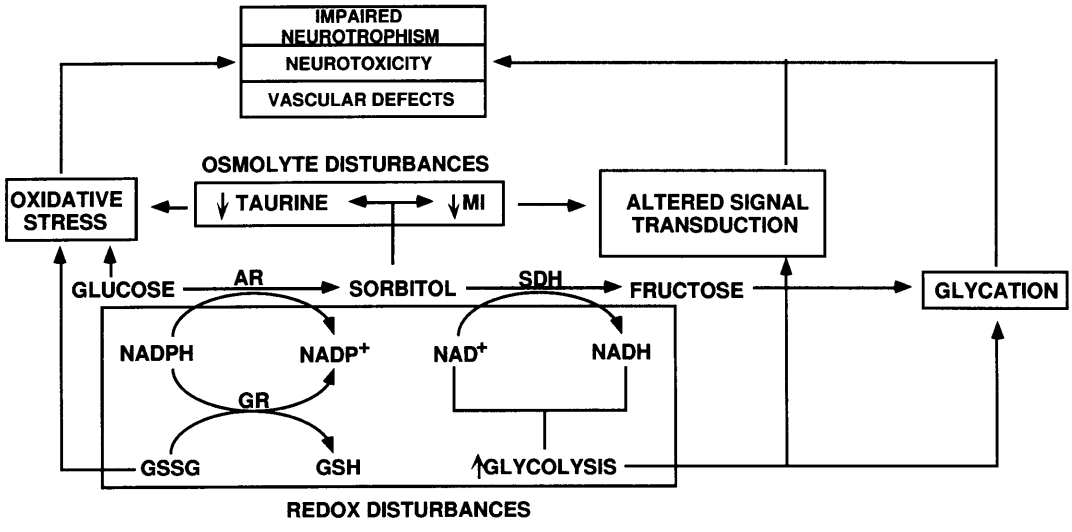

Figure 1. Hypothetical scheme by which glucose, through its metabolism via aldose reductase ("AR") and sorbitol dehydrogenase ("SDH") produces redox disturbances (below) affecting the glutathione reductase ("GR") and glycolysis, and osmolyte disturbances (above) affecting taurine and myo-inositol ("MI"). Shift of glutathione from the reduced ("GSH") to the oxidized ("GSSG") form combined with depletion of taurine (an endogenous anti-oxidant) and auto-oxidation of glucose promote oxidative stress. Depletion of myo-inositol and disturbed glycolysis impair signal transduction. Glycolytic disturbances and fructose accumulation promote non-enzymatic glycation. The combination of oxidative stress, impaired signal transduction and non-enzymatic glycation produce secondary vascular defects and impair neurotrophism, and produce direct neurotoxicity in peripheral nerve.

REFERENCES

1. Thomas, P.K. and Eliasson, S.G. (1984) In: Peripheral Neuropathy, P.J. Dyck, et al., W.B. Saunders Company, p. 1773.
2. (1986). Ann.Neurol. 19, 288.
3. The DCCT Research Group, (1993). N. Engl. J. Med. 329, 977.
4. The DCCT Research Group, (1995). Diabetes 44, 968.
5. The DCCT Research Group, (1995). Diab. Care 18, 361.
6. Knuiman, M.W., Welborn, T.A., McCann, V.J., Stanton, K.G. and Constable, I.J. (1986). Diabetes 35, 1332.
7. Dyck, P.J., Kratz, K.M., Karnes, J.L., et al. (1993). Neurol. 43, 817.

8. Franklin, G.M., Shetterly, S.M., Cohen, J.A., Baxter, J. and Hamman, R.F. (1994). Diab. Care 17, 1172.
9. Young, M.J., Boulton, A.J., Macleod, A.F., Williams, D.R. and Sonksen, P.H. (1993). Diabetologia 36, 150.
10. Maser, R.E., Steenkiste, A.R., Dorman, J.S., et al. (1989). Diabetes 38, 1456.
11. Thomas, P.K., Ward, J.D. and Watkins, P.J. (1982) In: Complications of Diabetes, H. Keen, J. Jarrett (eds.). Edward Arnold, London, p. 109.
12. Nathan, D.M. (1996). Ann. Int. Med. 124 ,86.
13. Stevens, M.J., Feldman, E.L. and Greene, D.A. (1995). Diabet. Med.
14. Cameron, N.E. and Cotter, M.A. (1995). J. Clin. Invest. 96, 1159.
15. Cameron, N.E., Cotter, M.A. and Hohman, T.C. (1996). Diabetologia 39, 172.
16. Fernyhough, P., Diemel, L.T., Brewster, W.J. and Tomlinson, D.R. (1995). J. Neurochem. 64, 1231.
17. Tomlinson, D.R., Willars, G.B. and Carrington, A.L. (1992). Pharmacol. Ther. 54, 151.
18. Greene, D.A., Arezzo, J. and Brown, M. (1996). Diabetes 45(Suppl. 2), 190A.
19. Greene, D.A. and Brown, M.B. (1995) In: Diabetic Neuropathy: New Concepts and Insights, N. Hotta, D.A. Greene, J.D. Ward, A.A.F. Sima, A.J.M. Boulton (eds.). Exerpta medica, Elsevier, Amsterdam p. 379.
20. Russell, J.W., Karnes, J.L. and Dyck, P.J. (1996). J. Neurol. Sci. 135, 114.
21. Stevens, M.J., Lattimer, S.A., Kamijo, M., Van Huysen, C., Sima, A.A. and Greene, D.A. (1993). Diabetologia. 36, 608.
22. Stevens, M.J., Dananberg, J., Feldman, E.L., et al. (1994). J. Clin. Invest. 94, 853.
23. Shindo, H., Thomas, T.P., Larkin, D.D., et al. (1996). J. Clin. Invest. 97, 736.
24. Shindo, H., Tawata, M., Aida, K. and Onaya, T. (1992). J. Clin. Endocrinol. Metab. 74, 393.
25. Yasuda, H., Sonobe, M., Yamashita, M., et al. (1989). Diabetes. 38, 832.
26. Lal, S., Szwergold, B.S., Taylor, A.H., et al. (1995). Archives of Biochemistry and Biophysics 318, 191.
27. Keen, H., Payan, J., Allawi, J., et al. (1993). Diab.Care 16, 8.