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Recombinant proinsulin-transferrin fusion protein as an insulin prodrug for the targeted inhibition of hepatic glucose production

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Abstract

Insulin acts on peripheral tissues such as muscles and adipocytes to increase glucose uptake and disposal, as well as in the liver to inhibit hepatic glucose production. An insulin analog with selective action in the liver is considered an optimal anti-diabetic therapeutic agent. We have recently reported the production and characterization of a recombinant proinsulin-transferrin fusion protein (ProINS-Tf). ProINS-Tf had no detectable activity in increasing glucose uptake when added to cultured adipocytes. However, a slow but sustained hypoglycemic effect of subcutaneously injected ProINS-Tf was observed in diabetic mice under fasting conditions. In cultured hepatoma cells, it was found that ProINS-Tf inhibited glucose production which was dependent on Tf receptor-mediated endocytosis. It was also demonstrated that the conversion of inactive ProINS-Tf to active INS-Tf occurred inside the TfR-recycling compartments. When intravenously administered, a lag time was observed in the hypoglycemic effect of ProINS-Tf, but not of the trypsin-pretreated ProINS-Tf, confirming that an in vivo activation of the fusion protein was required for its bioactivity. Furthermore, it was found that the expression of liver gluconeogenic/glycogenolytic enzymes in mice was inhibited 12 hours after the fusion protein treatment. Therefore, ProINS-Tf represents a novel insulin prodrug that exhibits a long-acting hypoglycemic activity with the targeted inhibition of hepatic glucose production.

Biography

Wei-Chiang Shen received his Ph.D. from Boston University and postdoctoral training at Harvard Medical School and Brandeis University. After spent 10 years as a faculty member at Boston University School of Medicine, he joined University of Southern California School of Pharmacy in 1987 and is currently John A. Biles Professor in Pharmaceutical Sciences. He has published more than 130 papers, 13 issued US patents, and the textbook *Immunology for Pharmacy Students*. Dr. Shen is a Fellow of AAPS and AAAS, and was the recipient of the 2002 Eurand Award (Grand Prize) for Outstanding Novel Research in Oral Drug Delivery.