

METHODS FOR TREATING DIABETES

TECHNICAL FIELD

The invention relates to the field of medicine, in particular the treatment of the symptoms of diabetes mellitus by administration of insulin-like growth factor I complexed to insulin-like growth factor binding protein-3 (IGF-I/IGFBP-3 complex).

BACKGROUND ART

Diabetes mellitus is a syndrome with interrelated metabolic, vascular, and neuropathic components. The metabolic syndrome, generally characterized by hyperglycemia, comprises alterations in carbohydrate, fat and protein metabolism caused by absent or markedly reduced insulin secretion and/or ineffective insulin action. The vascular syndrome consists of abnormalities in the blood vessels leading to cardiovascular, retinal and renal complications. Abnormalities in the peripheral and autonomic nervous systems are also part of the diabetic syndrome.

Growth factors are polypeptides which stimulate a wide variety of biological responses (e.g., DNA synthesis, cell division, expression of specific genes, etc.) in a defined population of target cells. A variety of growth factors have been identified, including the transforming growth factor beta (TGF- β) superfamily, which includes the TGF- β s (1-5 and others) as well as bone morphogenetic proteins (BMPs), activins, inhibins, and the like, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), insulin-like growth factor-I (IGF-I) and IGF-II.

IGF-I and IGF-II are related in amino acid sequence and structure, with each polypeptide having a molecular weight of approximately 7.5 kilodaltons (kD). IGF-I mediates the major effects of growth hormone, and thus is the primary mediator of growth after birth. Both IGF-I and IGF-II have insulin-like activities (hence their names), and are mitogenic (stimulate cell division) for the cells in neural tissue, muscle, reproductive tissue, skeletal tissue and a wide variety of other tissues. Unlike most growth factors, the IGFs are present in substantial quantity in the circulation, but only a very small fraction of this IGF is free in the circulation or in other body fluids. Most circulating IGF is bound to an IGF-binding protein called IGFBP-3.

Almost all IGF circulates in a non-covalently associated ternary complex composed of IGF-I or IGF-II, IGFBP-3, and a larger protein subunit termed the acid labile subunit (ALS). This ternary complex is composed of equimolar amounts of each of the three components. ALS has no direct IGF binding activity and appears to bind only to the IGF/IGFBP-3 binary complex. The ternary complex of IGF+IGFBP-3+ALS has a molecular weight of approximately 150 Kd. This ternary complex is alleged to function in the circulation "as a reservoir and a buffer for IGF-I and IGF-II preventing rapid changes in the concentration of free IGF" (Blum et al., 1991, "Plasma IGFBP-3 Levels as Clinical Indicators" in *Modern Concepts in Insulin-Like Growth Factors*, E. M. Spencer, ed., Elsevier, N.Y., pp. 381-393). The ternary complex is also believed to play an important role in the prevention of hypoglycemia due to high doses of IGF-I, by binding IGF-I/IGFBP-3 complex and restricting its distribution (Zapf et al., 1994, "Intravenously Injected Insulin-like Growth Factor (IGF) I/IGF Binding Protein-3 Complex Exerts Insulin-like Effects in Hypophysectomized, but Not in Normal Rats", *Clinical Investigation* 95:179-186).

Nearly all of the IGF-I, IGF-II and IGFBP-3 in the circulation is in complexes, so very little free IGF is detectable. Moreover, a high level of free IGF in blood is generally considered undesirable. The most commonly cited side effect of IGF-I administration is the induction of clinically significant hypoglycemia. IGF-I induces significant hypoglycemia (significant hypoglycemia is normally defined as a decrease in blood glucose of 30% or more) in humans at doses of 30 μ g/kg by intravenous administration and 100 μ g/kg by subcutaneous administration (Lieberman et al., 1992, "Effects of Recombinant Human Insulin-like Growth Factor-I (rhIGF-I) on Total and Free IGF-I Concentrations, IGF-Binding Proteins, and Glycemic Response in Humans", *J. Clin. Endocrinol. Metab.* 75(1):30-36; Guler et al., 1987, "Short-term Metabolic Effects of Recombinant Human Insulin-like Growth Factor I in Healthy Adults", *New England J. Med.* 317(3):137-140). Other frequently observed significant side effects of free IGF-I administration include edema, jaw pain, and hypophosphatemia.

Studies with IGF-I have suggested its utility in treating a wide variety of indications. Clemmons and Underwood (1994, "Uses of Human Insulin-like Growth Factor-I in Clinical Conditions" *J. Clin. Endocrinol. Metabol.* 79(1):4-6) have suggested that IGF-I may be useful for the treatment of catabolic states, such as can arise due to trauma, severe burns, and major surgery. Clemmons and Underwood (supra) also suggest the utility of IGF-I in the treatment of acute and chronic renal disorders. IGF-I may be useful for the treatment of lymphopoietic disorders (Clark et al., 1993, "Insulin-like Growth Factor I Stimulation of Lymphopoiesis" *J. Clin. Invest.* 92:540-548). IGF-I has also been suggested as potentially useful in the treatment of bone disorders, such as osteoporosis, as well as wound healing and peripheral nerve disorders (Delany et al., 1994, "Cellular and Clinical Perspectives on Skeletal Insulin-like Growth Factor I" *J. Cell. Biochem.* 55(3):328-333; Steenfos, 1994, "Growth Factors and Wound Healing" *Scand J. Plast. Reconstr. Surg. Hand Surg.* 28(2):95-105; Lewis et al., 1993, "Insulin-like Growth Factor I: Potential for Treatment of Motor Neuronal Disorders" *Exp. Neurol.* 124(1):73-88).

Because of its insulin-like effects (especially the induction of hypoglycemia), IGF-I has been studied for the treatment of diabetes, both type I juvenile, or insulin-dependent) and type II (adult, or insulin independent), as well as for the treatment of insulin resistance in both type I and type II diabetes.

U.S. Pat. No. 5,674,845 teaches the use of IGF-I for the treatment of type A diabetes, a rare form of insulin-resistant diabetes. U.S. Pat. No. 4,988,675 teaches the use of IGF-I, alone or in combination with insulin, for the type I and type II diabetics with insulin resistance. U.S. Pat. No. 5,466,670 teaches the use of IGF-I for the treatment of type I diabetes. None of these patents teaches or suggests the use of IGF-I/IGFBP-3 complex for the treatment of diabetes of any type.

U.S. Pat. No. 5,686,408 teaches the administration IGF-I in accordance with a particular dosing regimen for the treatment of insulin resistance. This patent teaches that IGF-I/IGFBP-3 complex would be disadvantageous for the treatment of diabetes, because IGFBP's have been shown to decrease the hypoglycemic and other side effects of IGF-I. Since it is well known to those skilled in the art that IGF-I, when complexed with IGFBP-3, no longer causes hypoglycemia, hypophosphatemia, edema or jaw pain, it would be expected that IGF-I/IGFBP-3 complex would not be able to lower insulin requirements in a manner similar to free IGF-I.