Chapter 2

Binding Proteins of Protein Therapeutics

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Numerous examples of binding proteins for protein therapeutics have been reported. Binding proteins have been shown to exist for insulinlike growth factors I and II, tissue plasminogen activator, growth hormone, deoxyribonuclease I, tissue factor, nerve growth factor, transforming growth factor-β I and II, as well as others. Binding proteins may have either inhibitory or stimulatory effects, may modulate efficacy at the cellular level, and may also affect the pharmacokinetics and metabolism of protein therapeutics. Furthermore, the relative importance of binding proteins may be species or disease state specific. It is also important to realize that binding proteins may play a different role in the regulation of proteins when physiological concentrations of proteins are involved compared to pharmacological doses of protein therapeutics. The pharmacology, physiology, regulation, and interactions of binding proteins with their target proteins will be discussed. This review chapter will focus on insulinlike growth factor, tissue plasminogen activator, and growth hormone.

1. HUMAN INSULINLIKE GROWTH FACTOR-I

The insulinlike growth factors (IGFs) resemble insulin in their structure and in many of their actions. Originally termed somatomedins because they...
were defined as mediators of the somatogenic actions of growth hormone (GH), these peptides are now termed IGF-I and IGF-II. In a classical view, the actions of the IGFs were presumed to be endocrine. However, the IGFs are synthesized and released by many tissues and cell types (Nissley and Rechler, 1984; Daughaday and Rotwein, 1989), and IGF concentrations of physiologically significant levels occur in the tissues, implying possible autocrine and paracrine functions as well (Ooi and Herington, 1990); IGF-I has been shown to mediate the effects of several hormones at the local level (Rutanen and Pekonen, 1990).

1.1. Structure

Human IGF-I is a basic plasma peptide (pI 8.4) with a molecular mass of 7649 Da (Rinderknecht and Humbel, 1978a). IGF-I contains 70 amino acid residues in a single chain with three disulfide bridges (Baxter, 1988). IGF-I is highly homologous to insulin with an amino-terminal region 29 amino acids in length which corresponds to the B chain of insulin. There is a sequence of 12 amino acids (corresponding to but not homologous to the proinsulin C-peptide) which links the amino-terminal region to a region 21 amino acids long which is homologous to the A chain of insulin. IGF-I differs from proinsulin in two ways: its C-peptide region is not cleaved, and it has an 8-amino-acid sequence, termed the D-peptide, at the carboxy terminus of the A-chain region (Rinderknecht and Humbel, 1978a,b).

1.2. Actions

IGF-I actions fall into three classes: metabolic activity, mitogenesis, and differentiation. The metabolic actions are principally anabolic and include insulinlike actions such as stimulation of glucose uptake, glycogen synthesis, amino acid transport, and protein synthesis. The injection of IGF-I into rats or humans elicits a hypoglycemic response similar to that caused by insulin, with about 7.5% of the potency of insulin on a molar basis (Guler et al., 1987).

The mitogenic activity of IGF-I has been well documented in many in vitro cell culture systems (Leof et al., 1982). Addition of IGF-I to growth media in these systems stimulates DNA synthesis and cellular proliferation (Riss et al., 1988). In vivo studies comparing IGF-I and growth hormone (GH) responses in hypophysectomized rats (Guler et al., 1988) have shown that IGF-I has effects on whole body growth, bone formation, and organ growth, specifically of the thymus, spleen, and kidney.