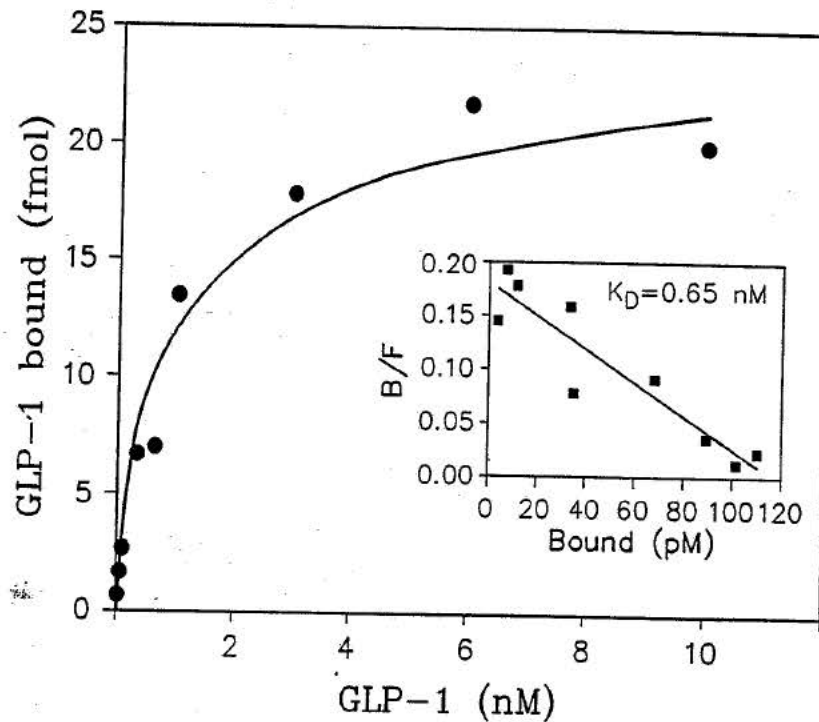




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(54) Title: RECEPTOR FOR THE GLUCAGON-LIKE-PEPTIDE-1 (GLP-1)



(57) Abstract

The present invention relates to a recombinant glucagon-like peptide-1 (GLP-1) receptor, to a DNA construct which comprises a DNA sequence encoding a GLP-1 receptor, to methods of screening for agonists of GLP-1 activity, and to the use of the GLP-1 receptor for screening for agonists of GLP-1 activity

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## RECEPTOR FOR THE GLUCAGON-LIKE-PEPTIDE-1 (GLP-1)

## FIELD OF THE INVENTION

The present invention relates to a recombinant glucagon-like peptide-1 (GLP-1) receptor, to a DNA construct which comprises a DNA sequence encoding a GLP-1 receptor, to methods of screening for agonists of GLP-1 activity, and to the use of the GLP-1 receptor for screening for agonists of GLP-1 activity.

## BACKGROUND OF THE INVENTION

As used in the present specification the designation GLP-1 comprises GLP-1(7-37) as well as GLP-1(7-36)amide.

Glucose-induced insulin secretion is modulated by a number of hormones and neurotransmitters. In particular, two gut hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP) potentiate the effect of glucose on insulin secretion and are thus called gluco-incretins (Dupre, in *The Endocrine Pancreas*, E. Samois Ed. (Raven Press, New York, (1991), 253 - 281) and Ebert and Creutzfeld, (*Diabetes Metab. Rev.* 3, (1987)). Glucagon-like peptide-1 is a gluco-incretin both in rat and in man (Dupre and Ebert and Creutzfeld, *vide supra*, and Kreymann et al. (*Lancet* 2 (1987), 1300)). It is part of the proglucagon molecule (Bell et al. *Nature* 304 (1983), 368) which is proteolytically processed in intestinal L cells to GLP-1(1-37) and GLP-1(7-36)amide or GLP-1(7-37) (Mojsov et al. (*J.Biol.Chem.* 261 (1986), 11880) and Habener et al.: *The Endocrine Pancreas* E. Samois Ed. (Raven Press, New York (1991), 53 - 71). Only the truncated forms of GLP-1 are biologically active and both have identical effects on insulin secretion in beta cells (Mojsov et al. *J.Clin.Invest* 79 (1987), 616) and Weir et al. (*Diabetes* 38 (1989), 338). They are the most potent gluco-incretins so far described and are

active at concentrations as low as one to ten picomolar. The stimulatory effect of these gluco-incretin hormones requires the presence of glucose at or above the normal physiological concentration of about 5 mM and is mediated by activation of adenylate cyclase and a rise in the intracellular concentration of cyclic AMP (Drucker et al. Proc.Natl.Acad.Sci. USA 84 (1987), 3434) and Göke et al. (Am.J.Physiol. 257 (1989), G397). GLP-1 has also a stimulatory effect on insulin gene transcription (Drucker et al. Proc.Natl.Acad.Sci. USA 84 (1987), 3434). In a rat model of non-insulin-dependent diabetes mellitus (NIDDM) is associated with a reduced stimulatory effect of GLP-1 on glucose-induced insulin secretion (Suzuki et al. Diabetes 39 (1990), 1320). In man, in one study, GLP-1 levels were elevated in NIDDM patients both in the basal state and after glucose ingestion; however, following a glucose load there was only a very small rise in plasma insulin concentration (Ørskov et al. J.Clin.Invest. 87 (1991), 415). A recent study (Nathan et al. Diabetes Care 15 (1992), 270) showed that GLP-1 infusion could ameliorate postprandial insulin secretion and glucose disposal in NIDDM patients. Thus, as a further step in understanding the complex modulation of insulin secretion by gut hormones and its dysfunction in diabetes, we isolated and characterized a complementary DNA for the beta cell GLP-1 receptor and showed that it is part of a new family of G-coupled receptors.

#### DESCRIPTION OF THE INVENTION

The present invention relates to a recombinant glucagon-like peptide-1 (GLP-1) receptor.

More preferably, the invention relates to a GLP-1 receptor which comprises the amino acid sequence shown in SEQ ID No. 1, or an analogue thereof binding GLP-1 with an affinity constant,  $K_D$ , below 100 nM, preferably below 10 nM. In the present

context, the term "analogue" is intended to indicate a naturally occurring variant (including one expressed in other animal species, in particular human) of the receptor or a "derivative" i.e. a polypeptide which is derived from the native GLP-1 receptor by suitably modifying the DNA sequence coding for the variant, resulting in the addition of one or more amino acids at either or both the C- and N-terminal ends of the native amino acid sequence, substitution of one or more amino acids at one or more sites in the native amino acid sequence, deletion of one or more amino acids at either or both ends of the native sequence or at one or more sites within the native sequence, or insertion of one or more amino acids in the native sequence.

In another aspect, the present invention relates to a DNA construct which comprises a DNA sequence encoding the GLP-1 receptor of the invention, as well as a recombinant expression vector carrying the DNA construct and a cell containing said recombinant expression vector.

In one embodiment of the invention, the GLP-1 receptor molecule may be provided in solubilised and/or reconstituted form.

In the present context "solubilised" is intended to indicate a receptor as present in detergent-solubilised membrane preparations. "Reconstituted" is intended to indicate a receptor solubilised in the presence of essential cofactors, e.g. G-protein. In this embodiment the receptor may be in a reconstituted micellar form.

The DNA construct of the invention encoding the GLP-1 receptor preferably comprises the DNA sequence shown in SEQ ID No. 1, or at least a DNA sequence coding for a functional analogue thereof binding GLP-1 with an affinity below 100 nM, preferably below 10 nM or a suitable modification thereof. Examples of suitable modifications of the DNA sequence are nucleotide

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