Treatment of Obesity

General

Obesity is a serious and growing public health problem, particularly since it has been linked to the onset of diseases such as dyslipidemia, hypertension, cardiovascular diseases, insulin resistance and type II diabetes. The prevalence of adult obesity has increased approximately 75% in the last quarter century. It is now estimated that 10% of the world's population are overweight or obese. As a result, new therapeutic options for the treatment of obesity-related disorders are clearly warranted.

State of the art

Gp130 receptor ligands are potential therapeutic targets for obesity-induced insulin resistance. In particular, gp130 receptor cytokines ciliary neurotropic factor (CNTF) and interleukin (IL)-6 enhance fat oxidation in skeletal muscle and increase insulin sensitivity *in vivo*. However, despite the major advances in the understanding as to how gp130 receptor ligands may enhance insulin sensitivity and act as "anti-obesogenic" agents, clinical trials have not been successful. This has been due principally to two major complications. The first is that IL-6 is pro-inflammatory and while it has positive effects on energy balance and insulin sensitivity, it has negative effects on the progression of many diseases. Secondly, CNTF failed in clinical trials because patients developed antibodies to the human recombinant variant of CNTF. Still further, due to the low level of CNTF receptors present in the periphery and the lower level of affinity of CNTF for the more light expressed IL-6 receptor, quite high concentrations of CNTF were required to be used.

The invention

The invention consists in a method of inducing lipid oxidation or increasing insulin sensitivity through the administration of a ligand which binds to the IL-6 receptor and signals via a gp130/LIF (leukemia inhibitory factor) receptor heterodimer. The unwanted side effects known to be associated with the administration of IL-6 and CNTF can be minimised by activating the IL-6 receptor and facilitating the induction of the subsequent signalling via a gp130/LIF receptor heterodimer, rather than the gp130 homodimer which is used by IL-6.
Such a chimeric gp130 receptor ligand may be created by combining IL-6 and CNTF (Fig 1). As such, the chimeric ligand possesses an IL-6 binding capacity while inducing CNTF signalling. It utilises the highly expressed IL-6 receptor to mediate the beneficial metabolic effects of CNTF while avoiding immunoreactivity. By combining the beneficial characteristics of CNTF and IL-6, the chimeric ligand has the potential to be a highly effective therapy for obesity.

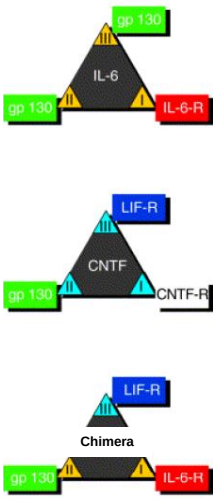

Figure 1. Chimeric gp130 receptor ligand produced by replacing one of the gp130 receptor binding sites in IL-6 with the LIF-R binding site from CNTF (adapted from Kallen et al. 2000, Trends Biotechnol).

Advantages

- new methodology for increasing lipid oxidation in mammals
- no induction of an inflammatory state
- no use of high concentrations of cytokine
- no generation of autoantibodies

Particularly useful in treating subjects suffering from symptoms caused by obesity, excessive appetite and overweight, as well as obesity-associated metabolic disorders such as hypertension, osteoarthritis, type II diabetes, increased blood pressure, stroke and heart disease.

Development stage

In vitro and first *in vivo* studies show promising results.

Patent status

AU2008234408 granted; US 13/968977, CA 2681935, EP 08733275 pending.

Utilisation concept

PVA SH GmbH is looking for industrial partners who are interested in licensing the invention.

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