

effects of the peptide on systemic inflammation (SIRS) during experimental human endotoxemia. At t = 0 hours, 2 ng/kg E. Coli endotoxin was administered i.v. followed by a 2-hour continuous i.v. infusion of tetrapeptide with SEQ ID NO: 2 (AQGV) or placebo. Levels of circulating cytokines and adhesion molecules as well as body temperature and flu-like symptoms were assessed.

The tetrapeptide with SEQ ID NO: 2 (AQGV) was well tolerated and showed an excellent safety profile. Treatment with at 180mg/kg (the highest dose) of the peptide, but not with the lower doses tested, resulted in a significant attenuation of the endotoxin induced increase in plasma levels of IL-6, IL-8, IL-1RA, MCP-1, MIP-1 α , and MIP-1 β and the adhesion molecule VCAM-1. Furthermore, the highest dose reduced fever and flu-like symptoms. It was concluded that administration of the tetrapeptide with SEQ ID NO: 2 (AQGV) is safe and results in attenuation of the systemic inflammatory response in humans. However, a drawback of the here above discussed di-, tri- and tetra-peptides for parenteral application is that they run the chance of being rapidly hydrolyzed in the blood before they have reached their target cells and can exert their beneficial actions. This rapid loss of peptide necessitates using high doses and long applications times to obtain the desired beneficial effects.

Summary

In one aspect, the present disclosure refers to use of a peptide comprising a dipeptide AQ and specifically recognizing an elastin receptor complex in the manufacture of a medicament for improving tissue repair comprising targeting cells having said complex associated with their surface, whereby said peptide is at least 7 amino acids and at most 30 amino acids comprising a sequence of the formula $\varphi n xGxxPG$, or $xGxxPG \varphi n$, or $\varphi n xGxxPG \varphi m$ wherein x is a naturally occurring amino acid, and φ is an autophagy inhibiting amino acid selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R).

In one aspect, the present disclosure refers to a pharmaceutical formulation comprising a peptide specifically recognizing an elastin receptor complex and comprising a dipeptide AQ whereby said peptide is at least 7 amino acids and at most 30 amino acids comprising a
5 sequence of the formula φ_n xGxxPG, or xGxxPG φ_n , or φ_n xGxxPG φ_m wherein x is a naturally occurring amino acid, and φ is an autophagy inhibiting amino acid selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R) and further comprising insulin.

In one aspect, the present disclosure refers to a pharmaceutical formulation comprising a peptide disclosed herein wherein φ is an autophagy inhibiting amino acid selected from the group leucine (L), alanine (A), glutamine (Q), glycine (G) and proline (P).

In one aspect, the present disclosure refers to a pharmaceutical formulation disclosed

5 herein for use in the treatment of impairment of pancreatic beta-cell function.

In one aspect, the present disclosure refers to use of a pharmaceutical formulation disclosed herein in the manufacture of a medicament for treating impairment of pancreatic beta-cell function.

In one aspect, the present disclosure refers to a method for producing a formulation

10 disclosed herein comprising synthesizing said peptide with an automated peptide synthesizer.

Description

15 According to the present invention the amino acids that have the beneficial effects are targeted to the cells in which they can have their beneficial effects, in particular by targeting the elastin receptor complex through any specific means. Preferably the targeting means enables internalization of the amino acids and when the amino acids are provided in an oligopeptide format said internalization typically results in the oligopeptide being delivered

20 to a lysosome (generally, and herein, also called autophagosome). Thus the invention provides a method for lowering autophagy, comprising targeting cells having an elastin receptor complex associated with their surface with a molecule specifically recognizing said complex, whereby said molecule is provided with a source of autophagy inhibiting amino acids, selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G),

25 valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R), more preferably selected from the group leucine (L), alanine (A), glutamine (Q), glycine (G) and proline (P). Said targeting then results in delivering said source, as a package of autophagy inhibiting amino acids, to the cell, where the molecule provided with said source or package is for example

Claims

1. Use of a peptide comprising a dipeptide AQ and specifically recognizing an elastin receptor complex in the manufacture of a medicament for improving tissue repair
5 comprising targeting cells having said complex associated with their surface, whereby said peptide is at least 7 amino acids and at most 30 amino acids comprising a sequence of the formula φ_n xGxxPG, or xGxxPG φ_n , or φ_n xGxxPG φ_m wherein x is a naturally occurring amino acid, and φ is an autophagy inhibiting amino acid selected from the group of alanine (in one letter code: A), glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I),
10 proline (P) and arginine (R).
2. The use according to claim 1 wherein φ is an autophagy inhibiting amino acid selected from the group leucine (L), alanine (A), glutamine (Q), glycine (G) and proline (P).
- 15 3. A pharmaceutical formulation comprising a peptide specifically recognizing an elastin receptor complex and comprising a dipeptide AQ whereby said peptide is at least 7 amino acids and at most 30 amino acids comprising a sequence of the formula φ_n xGxxPG, or xGxxPG φ_n , or φ_n xGxxPG φ_m wherein x is a naturally occurring amino acid, and φ is an autophagy inhibiting amino acid selected from the group of alanine (in one letter code: A),
20 glutamine (Q), glycine (G), valine (V), leucine (L), isoleucine (I), proline (P) and arginine (R) and further comprising insulin.
4. A pharmaceutical formulation comprising a peptide according to claim 3 wherein φ is an autophagy inhibiting amino acid selected from the group leucine (L), alanine (A),
25 glutamine (Q), glycine (G) and proline (P).
5. A pharmaceutical formulation according to claim 3 or 4 for use in the treatment of impairment of pancreatic beta-cell function.
- 30 6. A method for producing a formulation according to any of claim 3-5 comprising synthesizing said peptide with an automated peptide synthesizer.

7. Use of a pharmaceutical formulation according to any of claim 3-5 in the manufacture of a medicament for treating impairment of pancreatic beta-cell function.