main mechanisms involved in type 2 diabetes: insulin resistance (biguanides and thiazolidinediones) and insulin secretion (sulfonylureas, glinides, dipeptidylpeptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists), agents that delay absorption of glucose by gastrointestinal tract or promote weight loss and newer agents that promote renal glucose excretion. However, most of these medications have been shown to have deleterious side effects such as weight gain, peripheral edema or congestive heart failure and there is a major problem with a loss of effectiveness of these agents with long-term use. Thus, despite the increasing number of therapeutic options for glycaemic control, there is a need for alternative and improved medications for the treatment of diabetes and related conditions.

SUMMARY ~~**OF THE INVENTION**~~

Surprisingly, the inventors provide peptides from the kinase domain of the PKCα and derivatives thereof which specifically improves glucose tolerance in diet induced obese mice. The peptides are capable of decreasing the expression of Solute Carrier Family 27 Member 2 (SLC27A2) commonly known as FATP2 (Fatty acid transport protein 2) in adipose tissue. The peptides are capable of decreasing glycated albumin in plasma of an animal model, the glycated albumin being a well-known biomarker of diabetes.

In one aspect, the present disclosure relates to a use of a peptide in the manufacture of a medicament for treating diabetes and associated disorders selected from the group consisting of type I diabetes, type II diabetes, insulin resistance, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, hyperglycemia, obesity, hyperinsulinaemia and Bardet Biedl syndrome, wherein

- the peptide is capable of decreasing the FATP2 expression in adipose tissue;
- the peptide does not simultaneously comprise one methionine, one proline and one arginine;
- the peptide adopts a secondary structure which is a helix, preferably an alpha helix; and
- the peptide comprises at least 5 consecutive residues of the kinase domain of an αPKC (alpha Protein Kinase C);
- the peptide has a length from 5 to 60 amino acids, and
- the peptide sequence may comprise from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof within said sequence of a segment of the kinase domain of the PKC.

Accordingly, in one example, the present ~~invention~~disclosure relates to a peptide for use for treating diabetes and associated disorders, wherein

- the peptide is capable of decreasing specifically the FATP2 expression in adipose tissue, in particular in a mammal, especially human adipose tissue;
- the peptide does not simultaneously comprise one methionine, one proline and one arginine;
- the peptide adopts a secondary structure which is a helix, preferably an alpha helix; and
- the peptide comprises, consists essentially in or consists in a sequence from a segment of at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 25 consecutive residues of the kinase domain of a PKC (Protein Kinase C) or a segment from 5 to 40 consecutive residues of the kinase domain of a PKC (Protein Kinase C);
- the peptide has a length from 5 to 80 amino acids or from 5 to 60 amino acids or from 5 to 40 amino acids, and
- the peptide sequence may comprise 1, 2, 3, 4, or 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof within said sequence of a segment of the kinase domain of the PKC.

Preferably, the peptide is modified by a chemical cross-linking process such as stapling.

3 modification(s) of an amino acid selected from substitution(s) deletion(s), addition(s), and a mixture thereof.

Preferably, said PKC is selected from the group consisting of an alpha-PKC (αPKC), a beta-PKC (βPKC) including βI and βII PKC, delta-PKC, theta-PKC, eta-PKC and epsilon-PKC. More preferably, said PKC is an αPKC of SEQ ID NO: 1.

In a particular ~~embodiment~~example, the peptide sequence comprises, consists essentially in or consists in

VECTT**R**EKEVLA**S**LDKAAFLTQLHS (SEQ ID NO: 32)

wherein **R** and **S** carry the stapling, being preferably 2-(7-octenyl)arginine and 2-(4-pentenyl)serine, respectively;

with the sequence having optionally 1, 2, 3, 4, or 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof, more preferably, 1, 2, or 3 modification(s) of an amino acid selected from substitution(s) deletion(s), addition(s), and a mixture thereof.

The present ~~invention~~disclosure also relates to a pharmaceutical composition comprising a peptide according to the present disclosure for use for the treatment of diabetes and associated disorders. It further relates to the use of a peptide according to the present disclosure for the manufacture of a drug for the treatment of diabetes and associated disorders.

Optionally, diabetes and associated disorders are selected from the group consisting of type I diabetes, type II diabetes, insulin resistance, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, hyperglycemia, obesity, hyperinsulinaemia and Bardet Biedl syndrome. Optionally, the peptide is used in combination with one or more additional active drugs preferably selected from the group consisting of an anti-diabetic drug, a hypolipidemic agent, an anti-obesity agent, an anti-hypertensive agent, an anti-steatotic drug, an anti-inflammatory agent, and an agonist of peroxisome proliferator-activator receptors.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. PKC kinase activity in human adipocytes induced by peptides from alpha PKC.

Primary human adipocytes were cultured overnight without insulin and on the next day, the different conditions were used with for each peptide 25 ug of peptide ECTMVEKKVLALL or 25ug of peptide SVEWWAYGLLYEMLA was added to each well and incubated for 30 minutes prior to measuring the PKC activity. Vehicle which is saline solution was the negative control and the positive control used was insulin at 10 mM.

Figure 2. FATP isoform expression level of human adipocytes treated with the peptides derived from the human alpha PKC. Following 48 hours of incubation with the different

Claims

1. Use of a~~A~~ peptide in the manufacture of a m~~e~~dicament for ~~use for the treatment~~ treating ~~of~~ diabetes and associated disorders selected from the group consisting of type I diabetes, type II diabetes, insulin resistance, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, hyperglycemia, obesity, hyperinsulinaemia and Bardet Biedl syndrome, wherein

- the peptide is capable of decreasing the FATP2 expression in adipose tissue;

- the peptide does not simultaneously comprise one methionine, one proline and one arginine;

- the peptide adopts a secondary structure which is a helix, preferably an alpha helix; and

- the peptide comprises at least 5 consecutive residues of the kinase domain of an αPKC (alpha Protein Kinase C);

- the peptide has a length from 5 to 60 amino acids, and

- the peptide sequence may comprise from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof within said sequence of a segment of the kinase domain of the PKC.

2. The ~~peptide for~~ use according to claim 1, wherein the peptide is modified by a chemical cross-linking.

3. The ~~peptide for~~ use according to claim 1 or 2, wherein the peptide has a length of at least 5 amino acids and less than 40 amino acids, preferably a length of at least 5 amino acids and less than 30 amino acids, more preferably of at least 5 amino acids and less than 25 amino acids.

4. The ~~peptide for~~ use according to any one of claims 1 to 3, wherein the peptide is capable of decreasing or preventing the interaction between ALMS 1 and αPKC.

5. The ~~peptide for~~ use according to any one of claims 1-4, wherein the peptide sequence comprises one of the following sequences: VECTMVEKRVLA (SEQ ID NO: 3) optionally comprising from 1 to 5 modification(s) of an amino acid selected

from substitution(s), deletion(s), addition(s), and a mixture thereof; VECTXVEKRVLA (SEQ ID NO: 9) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; VECTMVEKXVLA (SEQ ID NO: 10) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; VECTXVEKXVLA (SEQ ID NO: 11) optionally comprising from 1, to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; LMYHIQQV (SEQ ID NO: 4) optionally comprising from 1 to 3 modification(s) of an amino acid selected from substitution(s) deletion(s), addition(s), and a mixture thereof; LXYHIQQV (SEQ ID NO: 12) optionally comprising from 1 to 3 modification(s) of an amino acid selected from substitution(s) deletion(s), addition(s), or a mixture thereof; LDN; SVDWWAYGVLLYEMLA (SEQ ID NO: 6) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; SVDWWAYGVLLYEXLA (SEQ ID NO: 13) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; SVXWWAYGLLYEMLA (SEQ ID NO: 52) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; EDEDELFQSIME (SEQ ID NO: 7) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; EDEDELFQSIXE (SEQ ID NO: 14) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; GERDVRE (SEQ ID NO: 8) optionally comprising from 1 to 3 modification(s) of an amino acid selected from substitution(s) deletion(s), addition(s), and a mixture thereof; GEXDVRE (SEQ ID NO: 15) optionally comprising from 1 to 3 substitution(s) deletion(s), addition(s), and a mixture thereof; GERDVXE (SEQ ID NO: 16) optionally comprising from 1 to 3 modification(s) of an amino acid selected from substitution(s) deletion(s), addition(s), and a mixture thereof; GEXDVXE (SEQ ID NO: 17) optionally comprising from 1 to 3 modification(s) of an amino acid selected from substitution(s) deletion(s), addition(s), or a mixture thereof; LDN; AFF; PDY; XDY; PEII (SEQ ID NO: 5); XEII (SEQ ID NO: 18); PAK; XAK; wherein X is any amino acid except M, P and R.

6. The ~~peptide for~~ use according to claim 5, wherein the peptide sequence comprises one of the following sequences: VECTMVEKRVLA (SEQ ID NO: 3) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; VECTXVEKRVLA (SEQ ID NO: 9) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; VECTMVEKXVLA (SEQ ID NO: 10) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; VECTXVEKXVLA (SEQ ID NO: 11) optionally comprising from 1, to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; SVDWWAYGVLLYEMLA (SEQ ID NO: 6) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; SVDWWAYGVLLYEXLA (SEQ ID NO: 13) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; or SVXWWAYGLLYEMLA (SEQ ID NO: 52) optionally comprising from 1 to 5 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof, wherein X is any amino acid except M, P and R.

7. The ~~peptide for~~ use according to anyone of claims 1-4, wherein the peptide sequence comprises one of the following sequences: VECTMVEKRVLA (SEQ ID NO: 3); VECTXVEKRVLA (SEQ ID NO: 9); VECTMVEKXVLA (SEQ ID NO: 10); VECTXVEKXVLA (SEQ ID NO: 11); LMYHIQQV (SEQ ID NO: 4); LXYHIQQV (SEQ ID NO: 12); SVDWWAYGVLLYEMLA (SEQ ID NO: 6); SVDWWAYGVLLYEXLA (SEQ ID NO: 13); EDEDELFQSIME (SEQ ID NO: 7); EDEDELFQSIXE (SEQ ID NO: 14); GERDVRE (SEQ ID NO: 8); GEXDVRE (SEQ ID NO: 15); GERDVXE (SEQ ID NO: 16); GEXDVXE (SEQ ID NO: 17); wherein X is any amino acid except M, P and R.

8. The ~~peptide for~~ use according to claim 7, wherein the peptide sequence comprises one of the following sequences: VECTMVEKRVLA (SEQ ID NO: 3); VECTXVEKRVLA (SEQ ID NO: 9); VECTMVEKXVLA (SEQ ID NO: 10); VECTXVEKXVLA (SEQ ID NO: 11); SVDWWAYGVLLYEMLA (SEQ ID NO: 6);

SVDWWAYGVLLYEXLA (SEQ ID NO: 13); or SVXWWAYGLLYEMLA (SEQ ID NO: 52), wherein X is any amino acid except M, P and R.

9. The ~~peptide for~~ use according to anyone of claims 1-4, wherein the peptide sequence comprises, consists essentially in or consists in at least one of the following sequences:

a) VECTXVEKXVLALLDKXXFLTQLHS (SEQ ID NO: 20) wherein X is any amino acid except M, P and R, optionally comprising from 1 to 5 or from 1 to 3 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof;

b) VECTMVEKRVLALLDKXXFLTQLHS (SEQ ID NO: 21) wherein X is any amino acid except M, P and R, optionally comprising from 1 to 5 or from 1 to 3 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof;

c) VECTXVEKRVLALLDKPPFLTQLHS (SEQ ID NO: 22) wherein X is any amino acid except M, P and R, optionally comprising from 1 to 5 or from 1 to 3 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof;

d) VECTMVEKXVLALLDKPPFLTQLHS (SEQ ID NO: 23) wherein X is any amino acid except M, P and R, optionally comprising from 1 to 5 or from 1 to 3 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof; and

e) a peptide comprising a sequence of any segment of at least 5 to 25 consecutive residues of any sequence a) to d).

10. The ~~peptide for~~ use according to any one of claims 1-7, wherein the peptide sequence comprises, consists essentially in or consists in one of the following sequences:

VECTMXEKRVLAX (SEQ ID NO: 24)

VECTXXEKRVLAX (SEQ ID NO: 25)

VECTMXEKXVLAX (SEQ ID NO: 26)

VECTXXEKXVLAX (SEQ ID NO: 27)

VECTXXEKXVLAXLDKXXFLTQLHS (SEQ ID NO: 28)

VECTMXEKRVLAXLDKXXFLTQLHS (SEQ ID NO: 29)

VECTXXEKRVLAXLDKPPFLTQLHS (SEQ ID NO: 30)

VECTMXEKXVLAXLDKPPFLTQLHS (SEQ ID NO: 31)

VECTTXEKEVLAXLDKAAFLTQHS (SEQ ID NO: 53)

VECTTXEKEVLAXLDKAAF (SEQ ID NO: 54)

VEGTTXEKEVLAXLDKAAF (SEQ ID NO: 55) and

ECTTXEKEVLAXL (SEQ ID NO 56)

ECTMXEKKVLAXL (SEQ ID NO 57)

wherein the residues which are bold and underlined X carry the stapling and is any amino acid derivative suitable for stapling; and

wherein X is any amino acid except M, P and R, with the sequence having optionally from 1 to 5 or from 1 to 3 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof.

11. The ~~peptide for~~ use according to any one of claims 5-8, wherein X is an amino acid favorable to an α-helix secondary structure, or an amino acid selected from the group consisting of A, D, N, C, G, Q, E, H, L, K, F, S, W and Y, or an amino acid selected from the group consisting of A, D, N, G, Q, E, H, L, K, F, S, W and Y.

12. The ~~peptide for~~ use according to any one of claims 1-11, wherein said PKC is an αPKC of SEQ ID NO: 1.

13. The ~~peptide for~~ use according to claim 10, wherein the first bold and underlined X is R and the second bold and underlined X is S and said R and S carry the stapling.

14. The ~~peptide for~~ use according to any one of claims 1-13, wherein the peptide sequence comprises VECTTREKEVLASLDKAAFLTQLHS (SEQ ID NO: 32)

wherein R and S carry the stapling; wherein the peptide optionally further comprises from 1 to 5 or from 1 to 3 modification(s) of an amino acid selected from substitution(s), deletion(s), addition(s), and a mixture thereof.

15. The ~~peptide for~~ use according to claim 13 or 14, comprising 2-(7-octenyl)arginine and 2-(4-pentenyl)serine.

16. The ~~peptide for~~ use according to any one of claims 1-15, wherein the peptide is used in combination with one or more additional active drugs preferably selected from the group consisting of an anti-diabetic drug, a hypolipidemic agent, an anti-obesity agent, an anti-hypertensive agent, an anti-steatotic drug, an anti-inflammatory agent, and an agonist of peroxisome proliferator-activator receptors.