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(54)名稱

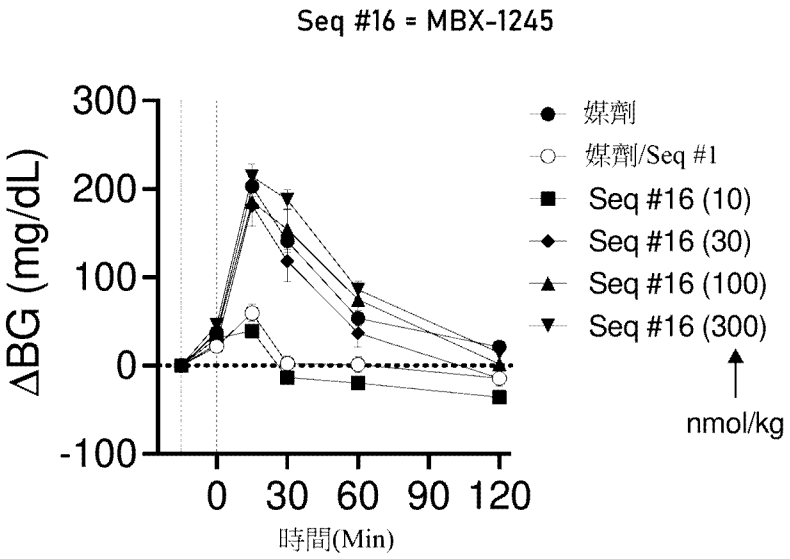
升糖素樣肽-1 受體拮抗劑

(57)摘要

本文提供用於治療低血糖症之 GLP-1 受體拮抗劑肽及醫藥組合物。本文進一步提供治療已變得具有高胰島素性之患者，包括在減重手術後變得具有高胰島素性之彼等患者之非典型低血糖症的方法。

Provided herein are GLP-1 receptor antagonists peptides and pharmaceutical compositions for the treatment of hypoglycemia. Further provided herein are methods of treating atypical hypoglycemia in patients that have become hyperinsulinemic, including those who become hyperinsulinemic after bariatric surgery.

指定代表圖：


Seq #16 = MBX-1245
300
200
100
0
-100
ΔBG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
媒劑/Seq #1
Seq #16 (10)
Seq #16 (30)
Seq #16 (100)
Seq #16 (300)
nmol/kg

【圖1】

【發明摘要】

【中文發明名稱】

升糖素樣肽-1受體拮抗劑

【英文發明名稱】

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR ANTAGONISTS

【中文】

本文提供用於治療低血糖症之GLP-1受體拮抗劑肽及醫藥組合物。本文進一步提供治療已變得具有高胰島素性之患者，包括在減重手術後變得具有高胰島素性之彼等患者之非典型低血糖症的方法。

【英文】

Provided herein are GLP-1 receptor antagonists peptides and pharmaceutical compositions for the treatment of hypoglycemia. Further provided herein are methods of treating atypical hypoglycemia in patients that have become hyperinsulinemic, including those who become hyperinsulinemic after bariatric surgery.

【指定代表圖】

圖1

【代表圖之符號簡單說明】

無

【發明說明書】

【中文發明名稱】

升糖素樣肽-1受體拮抗劑

【英文發明名稱】

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR ANTAGONISTS

【技術領域】

【先前技術】

【0001】 升糖素樣肽-1 (Glucagon-like peptide-1；GLP-1)在調節人類之血糖水平方面發揮重要作用。其作用包括刺激胰島素合成及分泌、抑制升糖素分泌及抑制食物攝入。通常，身體將血液中葡萄糖之濃度維持在約70至110毫克/分升(mg/dL)或3.9至6.1毫莫耳/公升(mmol/L)範圍內。然而，在葡萄糖水平變得過低從而導致低血糖症之情況可能出現多種病狀。低血糖症最通常係由用於控制糖尿病之藥物引起。少得多的低血糖症常見原因在本文中稱為「非典型低血糖症」，且可獨立於外源性胰島素投與發生。

【0002】 非典型低血糖症可在大量飲酒而不進食之人群中發生，因為酒精可阻斷肝臟中葡萄糖之形成。另外，患有晚期肝病，諸如病毒性肝炎、肝硬化或肝癌之人可能無法儲存及產生足夠葡萄糖。非典型低血糖症亦可導致嬰兒及兒童具有使得其呈高胰島素性之先天性突變。

【0003】 最近，在過去十年間期間，已越來越意識到非典型低血糖症為在出於逆轉極端肥胖形式之目的進行之手術程序後可產生的併發症。一些接受Roux-en-Y胃旁路術(RYGB)手術之患者(小於10%)隨後發展高胰島素性低血糖症，其中血糖濃度可變得足夠低(20-40 mg/dL)以引起癲

癇、心理狀態改變、喪失意識、認知功能異常、失能及死亡。

【0004】 一種治療高胰島素性誘導之低血糖症之途徑為投與GLP-1受體拮抗劑。此類肽拮抗劑阻斷經歷非典型低血糖症之患者中不適當升高濃度的血漿GLP-1刺激胰島素分泌之能力，且發揮使血漿葡萄糖正常且降低認知損傷、血管疾病功能及潛在猝死之風險的功能。

【0005】 艾塞那肽-4 (Exendin-4) (SEQ ID NO: 1)為升糖素樣肽1(GLP-1)受體之39胺基酸促效劑。艾塞那肽-4存在於吉拉毒蜥鈍尾毒蜥(*Heloderma suspectum*)之唾液中。Ex-4 (9-39)a (SEQ ID NO: 2)為已知用作GLP-1受體拮抗劑的艾塞那肽-4之N端截短衍生物。然而，Ex-4 (9-39)a關於其治療慢性非典型低血糖症之潛在用途具有兩個值得注意的限制：其非人類胺基酸序列及其相對較短的活體內作用持續時間。

【0006】 根據本發明之一個實施例，提供一組新穎最佳化GLP-1拮抗劑，其用作治療非典型低血糖症(包括在減重手術程序後引起或由先天性突變引起的高胰島素性誘導之低血糖症)中之候選藥物。

【發明內容】

【0007】 如本文所揭示，提供組合物及方法用於治療經歷非典型低血糖症的患者，且更特定言之在一個實施例中，治療經歷高胰島素血症誘導之低血糖症的患者。根據一個實施例，提供組合物及方法用於治療在減重手術後引起之高胰島素血症誘導的低血糖症。在一個實施例中該方法包含以有效提高血糖水平且緩解與低血糖症相關之相關急性症狀及慢性結果之量投與升糖素樣肽-1受體拮抗劑(GLP1RA)。

【0008】 根據一個實施例，提供一種GLP-1受體拮抗劑肽，其包含胺基酸序列 R_{10}-D$X_{10}X_{11}$RYL$X_{15}X_{16}$QAVREFX_{23}EWLVRGGPSSGAPPPS$X_{40}R_{20}$

(SEQ ID NO: 5)，其中

X_{10}為Trp、dTrp或Val；X_{11}為Trp、dTrp或Ser；X_{15}為Glu或dGlu

X_{16}為Trp、dTrp、dGlu或Glu；X_{23}為Ile或dIle；

X_{40}不存在或為醯化胺基酸，

R_{10}為NH_2、$-CO(CH_2)_{14-20}CH_3$或$-CO(CH_2)_{14-20}COOH$，及

R_{20}為COOH或$CONH_2$，視情況其中該肽相對於原生艾塞那肽4序列(SEQ ID NO: 1)在位置16、18、19、24、26或28中之任一者處包含一或多個Aib取代，或視情況相對於原生艾塞那肽4序列(SEQ ID NO: 1)在位置12處之Lys取代，視情況其限制條件為當X_{10}或X_{11}中之一者為Trp或dTrp時，另一者不為Trp或dTrp，視情況其限制條件為當X_{40}不存在時，R_{10}不為NH_2。在一個實施例中，提供一種SEQ ID NO: 5之GLP-1受體拮抗劑，其中X_{40}為醯化Lys，其中醯化Lys之醯基為視情況經由間隔子與Lys側鏈連接之C16-C18酸或二酸。

【0009】 在一個實施例中，提供一種GLP-1受體拮抗劑，其中該拮抗劑包含以下之胺基酸序列：

R_{10}-D$X_{10}X_{11}X_{12}$YL$X_{15}X_{16}$QAVREF$X_{23}X_{24}$WLVRGGPSSGAPPPS (SEQ ID NO: 98)；

其中

X_{10}為Trp、dTrp或Val；

X_{11}為Trp、dTrp或Ser；X_{12}為Arg、Lys或Ser；X_{15}為Glu或dGlu

X_{16}為Trp、dTrp、dGlu或Glu；X_{23}為Ile或dIle；

X_{24}為Ala或Glu；及

R_{10}為$-CO(CH_2)_{14-20}CH_3$或$-CO(CH_2)_{14-20}COOH$。

【0010】 根據一個實施例，提供一種GLP-1受體拮抗劑肽，其具有以下之胺基酸序列：

DVWRYLX$_{15}$EQAVREFIEWLVRGGPSSGAPPPSX$_{40}$R$_{20}$ (SEQ ID NO: 96)，

其中

X$_{15}$為dGlu；

X$_{40}$為醯化Lys且R$_{20}$為COOH或CONH$_2$，其中醯化Lys之醯基為視情況經由間隔子與Lys側鏈連接之C16-C18酸或二酸。在一個實施例中，間隔子包含minipeg或γ麩胺酸次單元，或此類minipeg或γGlu分子之任何多者或組合。在一個實施例中，SEQ ID NO: 96之肽經1、2或3個胺基酸取代修飾，包括例如相對於SEQ ID NO: 1之原生艾塞那肽4序列在位置16、18、19、24、26或28中之一或多者處經胺基異丁酸(Aib)的取代；或在位置12處的Lys取代。

【0011】 根據一個實施例，提供一種GLP-1受體拮抗劑肽，其包含以下胺基酸序列：

DX$_{10}$X$_{11}$RYLX$_{15}$X$_{16}$QAVREFX$_{23}$EWLVRGGPSSGAPPPSX$_{40}$R$_{20}$ (SEQ ID NO: 5)，其中

X$_{10}$為Trp、dTrp或Val；

X$_{11}$為Trp、dTrp或Ser；

X$_{15}$為Glu或dGlu

X$_{16}$為Trp、dTrp、dGlu或Glu；

X$_{23}$為Ile或dIle；

X$_{40}$為醯化胺基酸，且R$_{20}$為COOH或CONH$_2$，視情況其中該肽相對

於原生艾塞那肽4序列(SEQ ID NO: 1)在位置16、18、19、24、26或28中之任一者處包含一或多個Aib取代，或視情況SEQ ID NO: 5之肽之N端延伸部分，藉由X_7X_8，其中X_7為醯化胺基酸(例如Lys)且X_8為Gly或C_1-C_3 N-烷基Gly，其中位置編號相對於原生艾塞那肽4序列(SEQ ID NO: 1)，視情況其限制條件為當X_{10}或X_{11}中之一者為Trp或dTrp時，另一者不為Trp或dTrp。

【0012】 根據一個實施例，提供一種GLP-1受體拮抗劑肽，其具有以下之胺基酸序列：

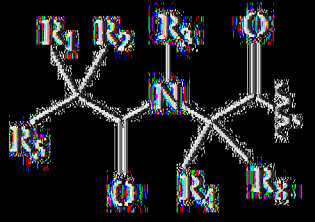
DVWRYLX$_{15}$EQAVREFIEWLVRGGPSSGAPPPSX$_{40}$ R$_{20}$ (SEQ ID NO: 96)，其中

X_{15}為dGlu；

X_{40}為醯化Lys且R_{20}為COOH或$CONH_2$，其中醯化Lys之醯基為視情況經由間隔子與Lys側鏈連接之C16-C18酸或二酸。在一個實施例中，間隔子包含minipeg或γ麩胺酸次單元，或此類minipeg或γGlu分子之任何多者或組合。在一個實施例中，SEQ ID NO: 96之肽經1、2或3個胺基酸取代修飾，包括例如相對於SEQ ID NO: 1之原生艾塞那肽4序列在位置16、18、19、24、26或28中之一或多者處經胺基異丁酸(Aib)取代；或藉由添加二肽X_7X_8至SEQ ID NO: 96之N端，其中X_7為醯化胺基酸(例如Lys)且X_8為Gly或C_1-C_3 N-烷基Gly，其中位置編號相對於原生艾塞那肽4序列(SEQ ID NO: 1)。

【0013】 在一個實施例中，將1至3個胺基酸添加至SEQ ID NO: 5之肽或其類似物之N端。在一個實施例中，構成N端延伸部分之胺基酸中之一者為醯化胺基酸。在一個實施例中，N端延伸部分為二肽X_7X_8，其中X_7

為醯化離胺酸，視情況其中離胺酸呈D構形且X_8為任何胺基酸。在一個實施例中，N端延伸部分為與9-29 艾塞那肽4類似物(例如SEQ ID NO: 5之肽)之N端α胺連接之自裂解二肽，以形成本發明之GLP-1拮抗劑中之任一者的前藥。使用GLP-1拮抗劑之前藥衍生物之一個優勢為，基於抑制GLP-1受體對前藥之識別的策略，此類途徑延長肽之生物半衰期。在一個實施例中，前藥衍生物包含與GLP-1拮抗劑共價連接之自裂解二肽(A-B)，其中二肽在生理條件下且在不存在酶活性下裂解以恢復GLP-1拮抗劑之全部活性。在一個實施例中，GLP-1拮抗劑藉由一或多個二肽(A-B)與GLP-1拮抗劑之胺之共價鍵聯經修飾，其中A為胺基酸或羥基酸，且B為經由B之羧基部分與GLP-1拮抗劑之胺之間的醯胺鍵與GLP-1拮抗劑連接的N-烷基化胺基酸。在一個實施例中，A-B包含以下結構：



其經由A-B之羧基與GLP-1拮抗劑之胺之間的醯胺鍵與GLP-1拮抗劑連接，其中

R_1、R_2、R_4及R_8獨立地選自由以下組成之群：H、C_1-C_{18}烷基、C_2-C_{18}烯基、(C_1-C_{18}烷基)OH、(C_1-C_{18}烷基)SH、(C_2-C_3烷基)SCH_3、(C_1-C_4烷基)$CONH_2$、(C_1-C_4烷基)COOH、(C_1-C_4烷基)NH_2、(C_1-C_4烷基)$NHC(NH_{2+})NH_2$、(C_0-C_4烷基)(C_3-C_6環烷基)、(C_0-C_4烷基)(C_2-C_5雜環)、(C_0-C_4烷基)(C_6-C_{10}芳基)R_7、(C_1-C_4烷基)(C_3-C_9雜芳基)及C_1-C_{12}烷基(W1)C_1-C_{12}烷基，其中W1為選自由N、S及O組成之群的雜原子；

R_3選自由以下組成之群：C_1-C_{18}烷基、(C_1-C_{18}烷基)OH、(C_1-C_{18}烷基)NH_2、(C_1-C_{18}烷基)SH、(C_0-C_4烷基)(C_3-C_6)環烷基、(C_0-C_4烷基)(C_2-

C_5雜環)、(C_0-C_4烷基)(C_6-C_{10}芳基)R_7及(C_1-C_4烷基)(C_3-C_9雜芳基)，或R_4及R_3與其所連接之原子一起形成吡咯啶環；

R_5為NHR_6或OH；

R_6為H、C_1-C_8烷基；及

R_7選自由H及OH組成之群，其中在生理條件下在PBS中，A-B自該GLP-1拮抗劑之化學裂解半衰期($t_{1/2}$)為至少約1小時至約1週。在一個實施例中，二肽A-B與GLP-1拮抗劑胺基酸序列之N端α胺共價連接。在一個實施例中，其中R_1為H、C_1-C_4烷基、(C_1-C_4烷基)OH或(C_1-C_4烷基)NH_2；R_2為H，R_3為C_1-C_6烷基；R_4為H、C_1-C_4烷基或(CH_2)(C_6芳基)R_7；R_5為NH_2；R_7為H或OH且R_8為氫。

【0014】 此外，本發明提供醫藥組合物，其包含本文所描述之GLP-1拮抗劑肽及變體肽中之任一者，以及醫藥學上可接受之載劑、稀釋劑或賦形劑。在一個實施例中，提供一種治療罹患非典型低血糖症患者之方法，其中該方法包含以有效提高血糖水平之量向有需要之患者投與醫藥組合物之步驟，該醫藥組合物包含本文所描述之GLP-1拮抗劑肽或變體肽。

【0015】 根據一個實施例，提供一種治療非典型低血糖症之方法，其中該方法包含以對增加血糖水平治療有效之量投與本文揭示之GLP-1受體拮抗劑肽中之任一者的步驟。在一個實施例中，GLP-1受體拮抗劑用具有足夠大小以以高親和力結合血清白蛋白之脂肪酸或二酸基團醯化。在一個實施例中，該方法包含投與醯化GLP-1受體拮抗劑，其中GLP-1拮抗劑用具有足夠大小以以高親和力結合血清白蛋白之脂肪酸或二酸基團醯化。在一個實施例中，GLP-1受體拮抗劑之N端α胺經醯化，視情況在C端進行第二醯化。在一個實施例中，GLP-1受體拮抗劑在C端經醯化，視情況其

中醯化胺基酸為C端胺基酸，且視情況GLP-1拮抗劑進一步藉由經由醯胺鍵鍵聯自裂解二肽經修飾，視情況其中二肽之胺基酸用具有足夠大小以以高親和力結合血清白蛋白之脂肪-醯基醯化。在一個實施例中，添加醯化胺基酸至SEQ ID NO: 11之位置40處的C端，且視情況所添加醯化胺基酸用C14-C20脂肪酸或脂肪二酸進行Lys醯化，其視情況經由本文揭示之間隔子中之任一者與胺基酸側鏈連接。

【0016】 在一個實施例中，用於治療非典型低血糖症之醫藥組合物包含本文所揭示之GLP-1受體拮抗劑中之任一者與適用於治療低血糖症之任何現有療法組合。舉例而言，醫藥組合物可包括本發明之GLP-1受體拮抗劑及以下中之一或多者：葡萄糖補充劑(例如右旋糖)；葡萄糖升高劑，諸如升糖素及升糖素類似物以及胰島素分泌抑制劑(例如二氮嗪、奧曲肽(octreotide))。

【圖式簡單說明】

【0017】

圖1為呈現在向小鼠皮下投與媒劑對照、Ex-4 (具有SEQ ID NO: 1之胺基酸序列的GLP-1促效劑)或GLP-1拮抗劑肽(DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK$_{40}$[mPEG-γE-C16]酸；SEQ ID NO: 16)，隨後腹膜內投與葡萄糖(1.5 g葡萄糖/kg體重)後，血糖水平隨著時間推移的劑量依賴性變化，其中在GLP-1拮抗劑後4小時皮下投與葡萄糖。

圖2A及圖2B呈現來自葡萄糖耐受性測試之資料，其中對小鼠皮下投與GLP-1拮抗劑，四小時後腹膜內投與葡萄糖(1.5 g葡萄糖/kg體重)。結果證明，SEQ ID NO: 16之GLP-1拮抗劑(圖2A)為完全拮抗劑且具有比GLP-1拮

抗劑Ex-9-40 (DVSKQMEEEAVRLFIEWLKNGGPSSGAPPPS；SEQ ID NO: 2)；圖2B)高得多的效能。

圖3呈現來自研究Aib取代對於GLP-1拮抗劑之功效之影響的葡萄糖耐受性測試之資料。對小鼠皮下投與GLP-1拮抗劑，四小時後腹膜內投與葡萄糖(1.5 g葡萄糖/kg體重)。圖3證明以下各者之活性：包含(SEQ ID NO: 47)之序列之9-40Jant4-K_{40} (DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK；SEQ ID NO: 3)的GLP-1拮抗劑肽類似物，及其包含一系列Aib取代的衍生物SEQ ID NO: 43 (Aib在位置20處)、SEQ ID NO: 44 (Aib在位置18處)、及SEQ ID NO: 45 (Aib在位置11處)、SEQ ID NO: 46 (Aib在位置10處)。

圖4呈現來自研究D-胺基酸取代對於GLP-1拮抗劑之功效之影響的葡萄糖耐受性測試之資料。對小鼠皮下投與GLP-1拮抗劑，四小時後腹膜內投與葡萄糖(1.5 g葡萄糖/kg體重)。如下各者之GLP-1拮抗劑活性：$(miniPEG)_2$-γE-C16醯化9-40Jant4-K_{40} (DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSX_{40} (SEQ ID NO: 12))肽SEQ ID NO:48，其中X_{40}為用$(miniPEG)_2$-γGlu-C16醯化之Lys，且具有C端醯胺，相對於媒劑對照；及包含取代及C端醯胺之變體，其中X_{40}為用C16醯化之Lys，其中呈D組態之對應胺基酸如下：SEQ ID NO: 49 (*d-Glu*^{15})、SEQ ID NO: 50 (*d-Val*^{19})、SEQ ID NO: 51 (*d-Ile*^{23})。

圖5A至圖5D提供關於本發明之GLP-1受體拮抗劑之前藥衍生物的資料。圖5A呈現隨著時間推移，在37℃下在PBS中培育之前藥dK_7(mPeg-γE-二酸C18) **N-Me-Gly**^{8}肽SEQ ID NO: 19之質量分光光度計資料。圖5B至圖5D為呈現在葡萄糖耐受性測試中，DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}；SEQ ID NO: 18之二肽前藥之GLP-1拮抗劑活性的圖，其中該肽已經共價連接的dK_7(mPeg-

γE-二酸C18) **N-iPr-Gly^{8}**二肽修飾，其中在投與拮抗劑後24 h (圖5B)、48 h (圖5C)或120 h (圖5D)投與葡萄糖刺激。

圖6A及圖6B提供關於包含兩個醯化胺基酸之本發明之GLP-1受體拮抗劑之衍生物的資料。圖6A及圖6B為呈現葡萄糖耐受性測試之結果的圖，其中在投與拮抗劑後24 h (圖6A)或48 h (圖6B)投與葡萄糖刺激，其中

SEQ ID NO: 16為R^{12}, E^{24}, R^{28}, K^{40}[mPEG-γE-C16]-(Jant4, 9-40)酸(SEQ ID NO: 16)；

SEQ ID NO: 17 為 dK^{7}(mPeg-γE(C18- 二 酸)**G^{8}**, R^{12}, E^{24},R^{28}, K^{40}[mPEG-γE- C16]-(Jant4, 9-40)酸(SEQ ID NO: 17)；

SEQ ID NO: 18 為dK^{7}(mPeg-γE(C18-二酸) **i-Pr,**G^{8}, R^{12},E^{24},R^{28}, K^{40}[mPEG-γE-C16]-(Jant4, 9-40)酸(SEQ ID NO: 18)；

SEQ ID NO: 19為dK^{7}(mPeg-γE(C18-二酸) **N-Me,**G^{8}, R^{12},E^{24},R^{28}, K^{40}[mPEG-γE-C16]-(Jant4, 9-40)酸(SEQ ID NO: 19)；

SEQ ID NO: 20 為 dK^{7}(**K**(mPeg-γE-C18 二 酸)$_2$ G^{8},R^{12},E^{24},R^{28} K^{40}[mPEG-γE- **C18二酸**] (Jant4, 9-40)醯胺(SEQ ID NO: 20)；

SEQ ID NO: 21 為 dK^{7}(**K**(mPeg-γE-C18 二 酸)$_2$ G^{8},R^{12},E^{24},R^{28} K^{40}[mPEG-γE- C16] (Jant4, 9-40)醯胺(SEQ ID NO: 21)；

SEQ ID NO: 22為dK^{7}(**K**(mPeg-γE-C18 二酸)$_2$ **N-Me,**G^{8},R^{12},E^{24},R^{28} K$_{40}$[mPEG-γE-C16] (Jant4, 9-40)醯胺(SEQ ID NO: 22)。

圖7提供根據本發明製備之各種N端醯化GLP-1拮抗劑之表(MBX 1391；SEQ ID NO: 118；MBX 1401；SEQ ID NO: 119；MBX 1402；SEQ ID NO: 120；MBX 1403；SEQ ID NO: 121；MBX 1404；SEQ ID

NO: 122；MBX 1406；SEQ ID NO: 123；MBX 1407；SEQ ID NO: 124；MBX 1408；SEQ ID NO: 125；MBX 1416；SEQ ID NO: 126)。所有此等GLP-1類似物亦在羧基端經醯化，除最終化合物MBX 1416之外，其僅在N端經醯化。

圖8為呈現如在24小時、48小時及72小時所量測之以四個不同劑量10 nmol/kg、30 nmol/kg、100 nmol/kg及300 nmol/kg皮下注射雙重醯化GLP-1拮抗劑(MBX 1407；SEQ ID NO: 116)之小鼠中之血糖水平的圖，其證明劑量依賴性反應。

圖9為呈現隨著時間推移，皮下注射300 nmol/kg雙重醯化GLP-1拮抗劑(MBX 1407；**X**-DVSSYLEEQAVREFIAWLV**R**GGPSSGAPPPS**O-**酸；SEQ ID NO: 116)與單醯化GLP-1拮抗劑(MBX 1342；DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSO-醯胺；SEQ ID NO: 117)之小鼠中之血糖水平的圖，其中X=C18-二酸且O=Lys(C18-二酸)。單位點脂化GLP-1拮抗劑比雙位點脂化GLP-1拮抗劑更強效。

圖10呈現如在使用過度表現GLP-1R之293細胞之活體外分析中所量測，各種GLP-1拮抗劑類似物(MBX 1342；SEQ ID NO: 127；MBX 1373；SEQ ID NO: 128；MBX 1416；SEQ ID NO: 126；MBX 1417；SEQ ID NO: 129；MBX 1418；SEQ ID NO: 130)之IC_{50} (奈莫耳)。

圖11A及圖11B為呈現隨著時間推移，皮下注射300 nmol/kg雙重醯化GLP-1拮抗劑(MBX 1407；圖11A)與單醯化GLP-1拮抗劑(MBX 1342；圖11B)之小鼠的體重變化之圖。單位點脂化GLP-1拮抗劑比雙位點脂化GLP-1拮抗劑更強效。

圖12呈現如在第2、4、7、9、11及14天所量測，隨著時間推移，皮

下注射100或300 nmol/kg未醯化GLP-1拮抗劑(MBX 1118 (Ex-9))、雙重醯化GLP-1拮抗劑(MBX 1407)及單醯化GLP-1拮抗劑(MBX 1416)之小鼠的血糖變化的資料。

圖13顯示在皮下注射100或300 nmol/kg未醯化GLP-1拮抗劑(MBX 1118 (Ex-9))、雙重醯化GLP-1拮抗劑(MBX 1407)及單醯化GLP-1拮抗劑(MBX 1416)後第14天進行之葡萄糖耐受性測試的結果。

【實施方式】

【0018】

相關申請案之交叉參考

本申請案主張2022年8月5日申請之美國臨時專利申請案第63/395,783號之優先權，其揭示內容明確地併入本文中。

【0019】

以引用之方式併入以電子方式提交的材料

本申請案含有序列表，該序列表已以電子方式以XML檔案格式提交且以全文引用之方式併入本文中。2023年8月1日創建之該XML複本命名為32993-392613_SL.xml，且大小為281千位元組。

【0020】

定義

在描述及主張本發明時，將根據下文所闡述之定義使用以下術語。

【0021】 如本文所用，術語「約」意謂比所陳述值或所陳述之值範圍大或小10%，但並不意欲將任何值或值範圍指定為僅此較寬定義。前面有術語「約」之各值或值範圍亦意欲涵蓋所陳述絕對值或值範圍的實施例。

【0022】 如本文所用，術語「胺基酸」涵蓋含有胺基與羧基官能基之任何分子，其中胺基及羧酸酯基連接至相同碳(α碳)。α碳視情況可具有一個或兩個其他有機取代基。胺基酸可藉由其三字母代碼、單字母代碼或在一些情況下藉由其側鏈名稱指示。舉例而言，包含與α碳連接之環己烷基的非典型胺基酸稱為「環己烷」或「環己基」。出於本發明之目的，未指定其立體化學之胺基酸名稱意欲涵蓋胺基酸之L或D形式，或外消旋混合物。然而，在其中胺基酸藉由其三字母代碼(亦即Lys)指示之情況下，此類名稱意欲指定胺基酸之原生L形式，而D形式將藉由在三字母代碼或單代碼之前包括小寫字母d來指定(亦即dLys或dK)。

【0023】 如本文所用，術語「羥基酸」係指已經修飾以用羥基置換α碳胺基之胺基酸。

【0024】 如本文所用，術語「非編碼胺基酸」涵蓋不為任一以下20種胺基酸之L-異構物的任何胺基酸：Ala、Cys、Asp、Glu、Phe、Gly、His、Ile、Lys、Leu、Met、Asn、Pro、Gln、Arg、Ser、Thr、Val、Trp、Tyr。

【0025】 「生物活性多肽」係指可在活體外及/或活體內發揮生物效應之多肽。

【0026】 如本文所用，一般提及肽意欲涵蓋具有經修飾之胺基及羧基端的肽。舉例而言，指示標準胺基酸之胺基酸序列意欲涵蓋在N端及C端之標準胺基酸以及在N端之對應羥基酸及/或經修飾以包含醯胺基代替末端羧酸之對應C端胺基酸。

【0027】 如本文所用，「醯化」胺基酸為包含對於天然存在之胺基酸為非原生的醯基(不管其以何種方式產生)的胺基酸。產生醯化胺基酸及

醯化肽之例示性方法為此項技術中已知，且包括在包含於肽或肽合成中之前醯化胺基酸，隨後化學醯化肽。在一些實施例中，醯基使肽具有以下中之一或多者：(i)循環半衰期延長，(ii)作用發作延遲，(iii)作用持續時間延長，(iv)對蛋白酶之抗性改善，及(v)針對GLP-1受體處之效能增加。

【0028】 如本文所用，「烷基化」胺基酸為包含對於天然存在之胺基酸為非原生的烷基(不管其以何種方式產生)的胺基酸。產生烷基化胺基酸及烷基化肽之例示性方法為此項技術中已知，且包括在包含於肽或肽合成中之前烷基化胺基酸，隨後化學烷基化肽。在不受任何特定理論限制之情況下，咸信，肽之烷基化將達成與肽之醯化類似(若不相同)的效果，例如循環半衰期延長、作用發作延遲、作用持續時間延長、對蛋白酶之抗性改善。

【0029】 如本文所用，術語「醫藥學上可接受之載劑」包括標準醫藥載劑中之任一者，諸如磷酸鹽緩衝鹽水溶液、水、乳液(諸如油/水或水/油乳液)，及各種類型之潤濕劑。該術語亦涵蓋經美國聯邦政府管制機構(regulatory agency of the US Federal government)批准或美國藥典(US Pharmacopeia)中列出供包括人類之動物使用之任何藥劑。

【0030】 如本文所用，術語「醫藥學上可接受之鹽」係指保留母體化合物之生物活性且在生物學上或其他方面無不合需要的化合物之鹽。許多本文所揭示之化合物藉助於胺基及/或羧基或其類似基團之存在而能夠形成酸式鹽及/或鹼式鹽。

【0031】 如本文所用，術語「親水性部分」係指易水溶或容易吸附水且在活體內為哺乳動物物種耐受而不具有毒性作用(亦即生物相容)之任何化合物。親水性部分之實例包括聚乙二醇(PEG)、聚乳酸、聚乙醇酸、

聚乳酸-聚乙醇酸共聚物、聚乙烯醇、聚乙烯吡咯啶酮、聚甲基噁唑啉(polymethoxazoline)、聚乙基噁唑啉、聚羥乙基甲基丙烯酸酯、聚羥基丙基甲基丙烯醯胺、聚甲基丙烯醯胺、聚二甲基丙烯醯胺及衍生纖維素(諸如羥甲基纖維素或羥乙基纖維素及其共聚物)，以及天然聚合物(包括例如白蛋白、肝素及聚葡萄糖)。

【0032】 如本文所用，術語「治療」包括緩解與特定病症或病狀相關之症狀，及/或預防或消除該等症狀。舉例而言，如本文所用，術語「治療低血糖症」將一般係指將血糖水平維持或增加至接近正常水平。

【0033】 如本文所用，GLP-1受體拮抗劑之「有效」量或「治療有效量」係指GLP-1拮抗劑提供所需作用之無毒性但足夠的量。舉例而言，一種所需作用將為預防或治療低血糖症。「有效」量將隨各個體而變化，視個體之年齡及一般狀況、投與模式及其類似因素而定。因此，不會一直指定確切「有效量」。然而，在任何個別情況下之適當「有效」量可由一般熟習此項技術者使用常規實驗來測定。

【0034】 術語「非經腸」意謂不經消化道，而藉由一些其他途徑，諸如鼻內、吸入、皮下、肌肉內、脊柱內或靜脈內。

【0035】 如本文所用，術語「衍生物」意欲涵蓋對化合物(例如胺基酸)之化學修飾，包括活體外化學修飾，例如藉由在多肽一或多個位置中之側鏈中引入基團(例如將硝基引入酪胺酸殘基中，或將碘引入酪胺酸殘基中)，或藉由將游離羧基轉化成酯基或醯胺基，或藉由利用醯化將胺基轉化成醯胺，或藉由醯化羥基而產生酯，或藉由烷基化一級胺而產生二級胺，或親水性部分與胺基酸側鏈鍵聯。藉由氧化或還原多肽中胺基酸殘基之側鏈來獲得其他衍生物。

【0036】 如本文所用，術語「一致性」係指兩個或更多個序列之間的相似性。藉由將一致殘基數目除以殘基總數且結果乘以100以達成百分比來量測一致性。因此，準確相同序列之兩個複本具有100%一致性，而相對於彼此具有胺基酸缺失、添加或取代之兩個序列具有較低一致性程度。熟習此項技術者將認識到若干電腦程式，諸如採用諸如鹼基局部比對檢索工具(Basic Local Alignment Search Tool，BLAST，Altschul等人(1993) J. Mol. Biol. 215:403-410)之演算法的電腦程式可用於測定序列一致性。

【0037】 如本文所用，分子針對第一受體相對於第二受體之術語「選擇性」係指以下比率：分子針對第二受體之EC_{50}除以分子針對第一受體之EC_{50}。舉例而言，針對第一受體之EC_{50}為1 nM且針對第二受體之EC_{50}為100 nM之分子針對第一受體相對於第二受體之選擇性為100倍。

【0038】 如本文所用，胺基酸「修飾」係指胺基酸取代，或藉由添加化學基團至胺基酸及/或自胺基酸移除化學基團之胺基酸衍生，且包括用在人類蛋白質中通常發現之20種胺基酸中之任一者，以及非典型或非天然存在之胺基酸取代。非典型胺基酸之商業來源包括Sigma-Aldrich (Milwaukee, WI)、ChemPep Inc. (Miami, FL)及Genzyme Pharmaceuticals (Cambridge, MA)。非典型胺基酸可購自商業供應商，重新合成，或經化學修飾或自天然存在之胺基酸衍生。

【0039】 如本文所用，胺基酸「取代」係指一個胺基酸殘基經不同胺基酸殘基置換。

【0040】 如本文所用，術語「保守胺基酸取代」在本文中定義為在以下五個群組中之一者內的交換：

I.小脂族、非極性或略微極性殘基：Ala、Ser、Thr、Pro、Gly；

II.極性、帶負電殘基及其醯胺：

Asp、Asn、Glu、Gln、氧化半胱胺酸及高氧化半胱胺酸；

III.極性、帶正電殘基：

His、Arg、Lys；鳥胺酸(Orn)

IV.大型、脂族、非極性殘基：

Met、Leu、Ile、Val、Cys、正白胺酸(Nle)、高半胱胺酸

V.大型、芳族殘基：

Phe、Tyr、Trp、乙醯基苯丙胺酸

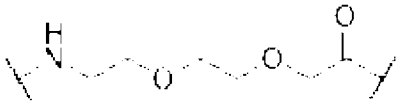
【0041】 在整個申請案中，所有藉由編號(例如位置28)提及特定胺基酸位置係指胺基酸在原生艾塞那肽4 (SEQ ID NO: 1)中之該位置或其任何類似物中之對應胺基酸位置處。舉例而言，本文中提及「位置28」將意謂其中SEQ ID NO: 1之第一胺基酸已缺失之艾塞那肽4之類似物的對應位置27。因此，9-39艾塞那肽4表示其中前8個胺基酸已缺失之N端截短艾塞那肽4肽。另外，提及大於39 (原生艾塞那肽4僅具有39個胺基酸)之位置意欲指在SEQ ID NO: 1之對應位置39後具有C端胺基酸延伸部分之類似物中的胺基酸位置。

【0042】 如本文所用，通用術語「聚乙二醇鏈」或「PEG鏈」係指由通式$H(OCH_2CH_2)_nOH$ (其中n 至少為2)表示之呈分支鏈或直鏈形式之環氧乙烷與水之縮合聚合物的混合物。「聚乙二醇鏈」或「PEG鏈」與數字後綴組合使用以指示其大致平均分子量。舉例而言，PEG-5,000係指具有約5,000道爾頓之平均總分子量的聚乙二醇鏈。

【0043】 如本文所用，術語「聚乙二醇化」及類似術語係指自其原

生狀態藉由將聚乙二醇鏈與化合物連接而經修飾之化合物。「聚乙二醇化多肽」為PEG鏈與共價結合多肽之多肽。

【0044】 如本文所用，術語「miniPEG」或「OEG」定義包含以下結構之官能化聚乙烯化合物：



【0045】 如本文所用，「連接子」或「間隔子」為使兩個單獨實體彼此結合之鍵、分子或分子群。連接子可向兩個實體提供最佳間隔或可進一步供應允許兩個實體彼此分離之不穩定鍵聯。不穩定鍵聯包括可光裂解基團、酸不穩定部分、鹼不穩定部分及酶可裂解基團。

【0046】 如本文所用，「二聚體」為包含兩個經由連接子彼此共價結合之次單元的複合物。當不存在任何限定性語言使用時，術語二聚體涵蓋同二聚體與異二聚體。同二聚體包含兩個相同次單元，而異二聚體包含兩個不同次單元，但兩個次單元彼此實質上類似。

【0047】 如本文所用，術語C16-C20脂肪酸指代結構：$CO(CH_2)_{14-20}CH_3$，且術語C16-C20二酸指代結構：$-CO(CH_2)_{14-20}COOH$，其中前綴「C16-C20」指代該名稱涵蓋之化合物中之可變碳總數。舉例而言，C18二酸表示結構：$-CO(CH_2)_{16}COOH$。如本文所用，對醯化胺基酸之一般提及涵蓋其側鏈經脂肪酸醯化的胺基酸及其側鏈經二酸醯化的胺基酸兩者。

【0048】 如本文所揭示之生理條件意欲包括約35至40℃之溫度及約7.0至約7.4之pH，且更典型地包括7.2至7.4之pH及36至38℃之溫度。因為生理pH及溫度在人類中在高度限定範圍內嚴格調節，所以自二肽/藥物複合物(前藥)轉化為藥物之速度將展現較高的患者內及患者間再現性。

【0049】 如本文所用，術語「C_1-C_n烷基」(其中n可為1至6)表示具

有一至指定數目個碳原子之分支鏈或直鏈烷基。典型C_1-C_6烷基包括但不限於甲基、乙基、正丙基、異丙基、丁基、異丁基、二級丁基、三級丁基、戊基、己基及其類似基團。

【0050】 如本文所用，術語「C_2-C_n烯基」(其中n可為2至6)表示具有2至指定數目個碳原子及至少一個雙鍵之烯烴不飽和分支鏈或直鏈基團。此類基團之實例包括但不限於1-丙烯基、2-丙烯基(-CH_2-CH=CH_2)、1,3-丁二烯基(-CH=CHCH=CH_2)、1-丁烯基(-CH=CHCH_2CH_3)、己烯基、戊烯基及其類似基團。

【0051】 如本文所用，術語「C_2-C_n炔基」(其中n可為2至6)係指具有2至n個碳原子及至少一個三鍵之不飽和分支鏈或直鏈基團。此類基團之實例包括但不限於1-丙炔基、2-丙炔基、1-丁炔基、2-丁炔基、1-戊炔基及其類似基團。

【0052】 如本文所用，術語「芳基」係指具有一個或兩個芳環之單環或雙環碳環環系統，包括但不限於苯基、萘基、四氫萘基、二氫茚基、茚基及其類似基團。芳基環之大小及取代基或連接基團之存在藉由指定存在碳之數目來指示。舉例而言，術語「(C_1-C_3烷基)(C_6-C_{10}芳基)」係指經由一至三員烷基鏈與母體部分連接之5至10員芳基。

【0053】 如本文所用，術語「雜芳基」係指含有一個或兩個芳族環且在芳族環中含有至少一個氮、氧或硫原子之單環或雙環環系統。雜芳基環之大小及取代基或連接基團之存在藉由指定存在碳之數目來指示。舉例而言，術語「」(C_1-C_n烷基)(C_5-C_6雜芳基)」係指經由一至「n」員烷基鏈與母體部分連接之5或6員雜芳基。

【0054】 如本文所用，術語「鹵基」係指由氟、氯、溴及碘組成之

群的一或多個成員。

【0055】 如本文所用，在無進一步指示之情況下，術語「患者」意欲涵蓋任何溫血脊椎動物馴養動物(包括例如但不限於家畜、馬、貓、狗及其他寵物)及人類，且不限於在醫師直接照護下之個體。

【0056】 如本文所用，術語「經分離」意謂已自其天然環境移出。

【0057】 如本文所用，術語「純化」係指分子或化合物呈實質上不含通常在原生或自然環境中與分子或化合物結合之雜質的形式分離，且意謂由於與原始組合物之其他組分分離，純度已增加。術語「純化的肽」在本文中用於描述已與其他化合物(包括但不限於核酸分子、脂質及碳水化合物)分離之肽。

【0058】 如本文所用，術語「肽」涵蓋2個或更多個胺基酸且通常小於50胺基酸之序列，其中胺基酸為天然存在或編碼或非天然存在或非編碼胺基酸。非天然存在之胺基酸係指不天然存在於活體內但仍可併入本文所描述之肽結構中的胺基酸。如本文所用，「非編碼」係指不為以下20種胺基酸中之任一者之L-異構物形式的胺基酸：Ala、Cys、Asp、Glu、Phe、Gly、His、Ile、Lys、Leu、Met、Asn、Pro、Gln、Arg、Ser、Thr、Val、Trp、Tyr。

【0059】 如本文所用，「部分非肽」係指其中分子之一部分為具有生物活性且不包含胺基酸序列之化合物或取代基的分子。

【0060】 「擬肽物」係指具有不同於現有肽之通式結構之結構，但以類似於現有肽之方式，例如藉由模擬該肽之生物活性起作用的化合物。擬肽物通常包含天然存在之胺基酸及/或非天然胺基酸，但亦可包含對肽主鏈之修飾。舉例而言，擬肽物可包括具有非肽部分(例如反向

retroinverso)片段)之插入或取代，或非肽鍵(諸如氮雜肽鍵(CO經NH取代)或假肽鍵(例如NH經CH_2取代)或酯鍵(例如縮肽，其中醯胺(-CONHR-)鍵中之一或多者經酯(COOR)鍵置換))之併入的天然存在之胺基酸之序列。或者，擬肽物可不含任何天然存在之胺基酸。

【0061】 如本文所用，術語「帶電胺基酸」或「帶電殘基」係指包含在水溶液中在生理pH值下帶負電(亦即，去質子化)或帶正電(亦即，質子化)之側鏈的胺基酸。舉例而言，帶負電胺基酸包括天冬胺酸、麩胺酸、氧化半胱胺酸、高氧化半胱胺酸及高麩胺酸，而帶正電胺基酸包括精胺酸、離胺酸及組胺酸。帶電胺基酸包括在人類蛋白質中通常發現之20種胺基酸以及非典型或非天然存在之胺基酸中的帶電胺基酸。

【0062】 如本文所用，術語「酸性胺基酸」係指包含第二酸性部分(除胺基酸之α羧酸以外)，包括例如側鏈羧酸或磺酸基之胺基酸。

【0063】 如本文所用，術語「前藥」定義為在展現其完全藥理作用前經歷化學修飾之任何化合物。

【0064】 如本文所用，「二肽」為α-胺基酸或α-羥基酸經由肽鍵與另一胺基酸鍵聯之結果。

【0065】 如本文所用，不存在任何其他指示之術語「化學裂解」涵蓋導致共價化學鍵斷裂之非酶促反應。

【0066】 如本文所用，術語「非典型低血糖症」限定患者中存在之與外源性胰島素投與無關的低血糖症病狀。

【0067】

縮寫：

小寫字母k =離胺酸之D-異構物

大寫字母K =離胺酸之L-異構物

γE = γ麩胺酸之L-異構物

$(miniPEG)_2 = COCH_2OCH_2CH_2OCH_2CH_2NH$

$COC_{16}H_{32}CO_2H$ = (C18二酸)

(N-Me)G =肌胺酸

【0068】

實施例

根據本發明之一個實施例，提供組合物及方法用於治療罹患與外源性胰島素投與無關之低血糖病狀(亦即非典型低血糖症)之患者。根據本發明，以足夠增加血糖水平及/或緩解與低血糖症相關之相關急性症狀及慢性結果之量，向罹患非典型低血糖症患者投與包含GLP-1拮抗劑的組合物。在一個實施例中，經歷非典型低血糖症之患者亦具有高胰島素血症病狀。在一個實施例中，高胰島素性病狀發生在患者接受減重手術之後。

【0069】 根據一個實施例，治療罹患非典型低血糖症之患者之方法包含投與醯化GLP-1受體拮抗劑肽，其中GLP-1受體拮抗劑肽在N端及/或C端經具有足夠大小以以高親和力結合血清白蛋白之脂肪酸或脂肪二酸基團醯化。在一個實施例中，C14-C20醯基與GLP-1受體拮抗劑肽之N端α胺共價連接。

【0070】 在一個實施例中，GLP-1受體拮抗劑在GLP-1受體拮抗劑之N端醯化，視情況其中乙醯基與升糖素肽之N端α胺共價連接。醯化升糖素肽之醯基可具有任何大小，例如任何長度碳鏈，且可為直鏈或分支鏈。在本發明之一些具體實施例中，醯基為C12至C30脂肪酸或脂肪二酸。舉例而言，醯基可為以下中之任一者：C12脂肪酸/二酸、C14脂肪酸/二

酸、C16脂肪酸/二酸、C18脂肪酸/二酸、C20脂肪酸/二酸、C22脂肪酸/二酸、C24脂肪酸/二酸、C26脂肪酸/二酸、C28脂肪酸/二酸、或C30脂肪酸/二酸。在一些實施例中，醯基為C14至C20脂肪酸，例如C14脂肪酸或脂肪二酸、C16脂肪酸或脂肪二酸、或C16脂肪酸或脂肪二酸。

【0071】 根據一個實施例，醯化GLP-1受體拮抗劑肽包含胺基酸序列DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK (SEQ ID NO: 3)或與SEQ ID NO: 3具有至少95%序列一致性同時保留GLP-1受體拮抗劑活性之其類似物。

【0072】 根據一個實施例，本發明之醯化GLP-1受體拮抗劑肽包含肽DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK (SEQ ID NO: 3)之類似物，其中GLP-1受體拮抗劑與SEQ ID NO: 3相差1、2、3、4、5、6、7、8、9或10個胺基酸修飾，其中該等修飾選自對於胺基酸結構之胺基酸取代、添加或修飾，包括但不限於C端胺基酸之醯化及/或醯胺化。在一個實施例中，胺基酸修飾為在肽之位置12、16、18、19、24、26、27及28中之一或多者處的胺基酸取代；及/或在位置15、16、17、19、20、21及23 (編號相對於原生艾塞那肽4 (SEQ ID NO: 1))中之一或多者處經d-異構物取代。在一個實施例中，SEQ ID NO: 3之類似物進一步藉由用C16-C18脂肪酸或二酸醯化C端胺基酸側鏈(視情況經由間隔子)修飾。

【0073】 根據一個實施例，提供一種GLP-1受體拮抗劑，其包含胺基酸序列DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK (SEQ ID NO: 4)，或與SEQ ID NO: 4相差1、2、3、4或5個胺基酸取代同時保留GLP-1受體拮抗劑活性之胺基酸序列，其限制條件為GLP-1拮抗劑肽不包含SEQ ID NO: 3之序列。在一個實施例中，提供一種肽，其與SEQ ID NO: 4之肽

相差以下中之一或多者：

i.在位置7、10、11、13或16中之任一者處之1、2或3個胺基酸經Trp或dTrp取代；

ii.在位置15、16或23中之任一者處之1、2或3個胺基酸經D構形中之對應胺基酸取代；

iii.在位置16、18、19、24、26或28中之任一者處之1、2或3個胺基酸經Aib取代；

iv.在位置12處經醯化胺基酸(視情況醯化離胺酸)取代；

v.在位置16處經dGlu、Asp、高麩胺酸或高氧化半胱胺酸取代；

vi.在位置19處經環丙烷、環戊烷、環己烷或苯基甘胺酸取代；

vii.在位置20處經dArg、高離胺酸或瓜胺酸取代；

viii.原生C端羧基經醯胺取代；

ix.添加1至3個胺基酸之N端延伸部分，視情況其中N端延伸部分胺基酸中之一者經醯化；

x. C端胺基酸經醯化胺基酸取代；

xi. i)至x)之任何組合。

【0074】 根據一個實施例，提供一種GLP-1受體拮抗劑，其包含胺基酸序列R_{10}-DV$X_{11}X_{12}$YL$X_{15}X_{16}$QA$X_{19}X_{20}$EFX_{23}EWLVRGGPSSGAPPPSX_{40}-R_{20} (SEQ ID NO: 23)，其中

R_{10}為NH_2、-$CO(CH_2)_{14-20}CH_3$、-$CO(CH_2)_{14-20}$COOH或1、2或3個胺基酸之N端延伸部分，其中N端延伸部分之胺基酸中之一者經C16-C18脂肪酸或二酸醯化(視情況經由間隔子)，視情況其中R_{10}為結構：X_7X_8之二肽，其中X_7為醯化胺基酸，視情況為醯化Lys或醯化dLys，且X_8為Gly或

C_1-C_4 N-烷基化Gly；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg或醯化胺基酸，視情況為醯化Lys；

X_{15}為Glu或dGlu；

X_{16}為Glu、dGlu、Asp、高麩胺酸或高氧化半胱胺酸；

X_{19}為Val、環丙烷、環戊烷、環己烷或苯基甘胺酸；

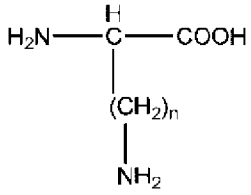
X_{20}為Arg、高離胺酸或瓜胺酸；

X_{23}為Ile或dIle；

X_{40}為醯化胺基酸，視情況為醯化Lys；及

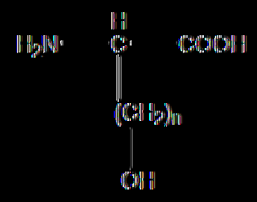
R_{20}為COOH或$CONH_2$，視情況其中1、2或3個選自位置7、10、13或16之胺基酸經Trp或dTrp取代，視情況其中限制條件為位置10及11不均為Trp或dTrp；視情況其中限制條件為R_{10}及X_{12}不均包含醯化胺基酸；視情況其中在位置16、18、19、24、26或28中之任一者處之1、2或3個胺基酸經Aib取代。

【0075】 在一個實施例中，SEQ ID NO: 23之肽之位置7、12及40中僅一者包含醯化胺基酸。在一個實施例中，SEQ ID NO: 23之肽之位置7、12及40中之兩者包含醯化胺基酸。在一個實施例中，在位置7、12及40處之醯化胺基酸獨立地為包含式I (視情況，Lys)或式II (視情況，Ser)之結構的胺基酸，其中式I及II中之各者為：



其中n= 1至4

[式I]及



其中n：1至4

[式II]

[0076] 在一個實施例中，提供一種SEQ ID NO: 23之肽，其中R_{10}為X_7X_8，其中X_7為醯化Lys或醯化dLys，X_{12}為Arg，且X_{40}為醯化Lys。在一個實施例中，提供一種SEQ ID NO: 23之肽，其中R_{10}為NH_2，X_{12}為醯化Lys，且X_{40}為醯化Lys。在一個實施例中，提供一種SEQ ID NO: 23之肽，其中R_{10}為NH_2，X_{12}為Arg，且X_{40}為醯化Lys。在一個實施例中，SEQ ID NO: 23之肽之醯化胺基酸為醯化Lys殘基，視情況其中醯化Lys殘基獨立地經C14-C24脂肪酸或脂肪二酸、或C16-C18脂肪酸或脂肪二酸醯化，視情況其中脂肪酸或脂肪二酸經由本文所揭示之間隔子分子中之任一者與Lys殘基之側鏈連接。

[0077] 根據一個實施例，提供一種GLP-1受體拮抗劑，其包含胺基酸序列R_{10}-DV$X_{11}X_{12}$YLEX_{16}QAVREFIEWLVRGGPSSGAPPPSX_{40}-R_{20} (SEQ ID NO: 24)，其中

R_{10}為NH_2-$CO(CH_2)_{14-20}CH_3$、-$CO(CH_2)_{14-20}COOH$或結構：X_7X_8之二肽，其中X_7為醯化胺基酸，視情況為醯化Lys或醯化dLys，且X_8為Gly或C_1-C_4 N-烷基化Gly；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg或醯化胺基酸，視情況為醯化Lys；

X_{16}為Glu或Asp；

X_{40}為醯化胺基酸，視情況為醯化Lys；及

R_{20}為COOH或$CONH_2$，視情況其中1、2或3個選自位置16、17、18、20或21之胺基酸經D構形中之對應胺基酸取代，及/或在位置16、18、19、24、26或28中之任一者處之1、2或3個胺基酸經Aib取代。

【0078】 根據一個實施例，提供一種GLP-1受體拮抗劑，其包含胺基酸序列 R_{10}-DV$X_{11}X_{12}$YLEX_{16}QAVREFIEWLVRGGPSSGAPPPSX_{40}-R_{20} (SEQ ID NO: 24)，其中

R_{10}為結構：X_7X_8之二肽，其中X_7為醯化Lys或醯化dLys，且X_8為Gly或肌胺酸；

X_{11}為Trp或dTrp；

X_{12}為Arg；

X_{16}為Glu；

X_{40}為醯化Lys；及

R_{20}為COOH或$CONH_2$，其中肽之該等醯化Lys殘基獨立地經C16-C18脂肪酸或脂肪二酸醯化(視情況經由如本文所揭示之間隔子)，視情況其中在位置16、18、19、24、26或28中之任一者處之1、2或3個胺基酸經Aib取代。

【0079】 在一個實施例中，提供一種GLP-1受體拮抗劑，其中該拮抗劑包含以下之胺基酸序列：

D$X_{10}X_{11}X_{12}$YL$X_{15}X_{16}$QAVREF$X_{23}X_{24}$WLVRGGPSSGAPPPS (SEQ ID NO:98)；

其中

X_{10}為Trp、dTrp或Val；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg、Lys或Ser

X_{15}為Glu或dGlu

X_{16}為Trp、dTrp、dGlu或Glu；

X_{23}為Ile或dIle；

X_{24}為Ala或Glu；

及

該GLP-1受體拮抗劑經具有足夠大小以以高親和力結合血清白蛋白之脂肪酸或二酸基團醯化，視情況其中GLP-1受體拮抗劑之胺基酸經C16-C18脂肪酸或C16-C18脂肪二酸醯化。

【0080】 在一個實施例中，提供一種GLP-1受體拮抗劑，其中該拮抗劑包含以下之胺基酸序列：

R_{10}-D$X_{10}X_{11}X_{12}$YL$X_{15}X_{16}$QAVREF$X_{23}X_{24}$WLVRGGPSSGAPPPS-R_{20} (SEQ ID NO: 98)，或與SEQ ID NO: 98相差1或2個胺基酸取代之序列；

其中

X_{10}為Trp、dTrp或Val；

X_{11}為Trp、dTrp或Ser；X_{12}為Arg、Lys或Ser X_{15}為Glu或dGlu

X_{16}為Trp、dTrp、dGlu或Glu；X_{23}為Ile或dIle；

X_{24}為Ala或Glu；

R_{10} 為 NH_2 、 $-CO(CH_2)_{14-20}CH_3$ 或 $-CO(CH_2)_{14-20}COOH$ ； 且 R_{20} 為COOH或$CONH_2$。在一個實施例中，提供SEQ ID NO: 98之序列，其中

X_{10}為Val；

X_{11}為Trp、dTrp或Ser；X_{12}為Arg、Lys或Ser X_{15}為Glu或dGlu

X_{16}為dGlu或Glu；X_{23}為Ile；

X_{24}為Ala或Glu；

R_{10}為-$CO(CH_2)_{14-20}CH_3$或-$CO(CH_2)_{14-20}COOH$，及

R_{20}為COOH，視情況其中肽相對於原生艾塞那肽4序列(SEQ ID NO: 1)在位置16、18、19、24、26或28中之任一者處包含一或多個Aib取代。

【0081】在一個實施例中，提供一種GLP-1受體拮抗劑，其中該拮抗劑包含以下之胺基酸序列：

R_{10}-$DX_{10}X_{11}X_{12}YLX_{15}X_{16}QAVREFX_{23}X_{24}$WLVRGGPSSGAPPPS-$R_{20}$ (SEQ ID NO: 98)；

其中

X_{10}為Val；

X_{11}為Ser；

X_{12}為Arg；

X_{15}為Glu或dGlu

X_{16}為dGlu或Glu；

X_{23}為Ile；

X_{24}為Glu；及

R_{10}為-$CO(CH_2)_{14-20}CH_3$或-$CO(CH_2)_{14-20}COOH$，及

R_{20}為COOH或$CONH_2$。

【0082】在一個實施例中，GLP-1拮抗劑肽包含胺基酸序列R_{10}-DVSSYLEEQAVREFIAWLVKGGPSSGAPPPS (SEQ ID NO: 3)，或與SEQ ID NO: 3相差1、2或3個胺基酸取代同時保留GLP-1促效劑活性之胺基酸序列，其中R_{10}為與SEQ ID NO: 3之胺基酸序列之N端α胺連接之-

$CO(CH_2)_{14-20}CH_3$或-$CO(CH_2)_{14-20}COOH$，且R_{20}為COOH或$CONH_2$，視情況其中R_{20}為COOH。

【0083】在一個實施例中，GLP-1拮抗劑肽包含胺基酸序列$DVX_{11}RYLQX_{15}X_{16}AVREFX_{23}EWLVRGGPSSGAPPPSX_{40}$-$R_{20}$ (SEQ ID NO: 25)，其中

X_{11}為Trp、dTrp或Ser；

X_{15}為Glu或dGlu；

X_{16}為Glu或dGlu；

X_{23}為Ile或dIle；

X_{40}為醯化胺基酸，視情況為經C16-C18脂肪酸或二酸醯化之Lys (視情況經由間隔子)；及

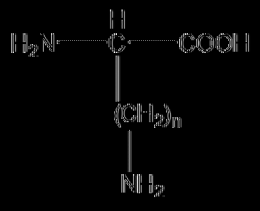
R_{20}為COOH或$CONH_2$。視情況，SEQ ID NO: 25之GLP-1拮抗劑相對於SEQ ID NO: 1之原生艾塞那肽4序列之編號進一步經位置16、18、19、24、26或28中之任一者處之一或多個Aib取代修飾，或進一步視情況經位置12處的醯化Lys取代修飾。在一個實施例中，提供一種SEQ ID NO: 25之肽，其進一步包含在位置12處的醯化Lys取代及視情況選用之在位置27處的Aib取代。

【0084】在一個實施例中，GLP-1拮抗劑肽包含以下之胺基酸序列：

$DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}R_2$ (SEQ ID NO: 6) 或 $X_7X_8DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}R_{20}$ (SEQ ID NO:26)，其中X_7為醯化Lys或醯化dLys，且X_8為Gly或肌胺酸，X_{11}為Trp或dTrp，X_{40}為醯化胺基酸，視情況為醯化Lys，其中醯化Lys殘

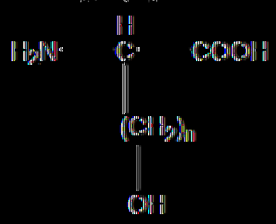
其包含視情況經由間隔子與Lys側鏈共價連接之C16-C18脂肪酸或二酸，且R_{20}為COOH或$CONH_2$。視情況，其於原生艾塞那肽4 (SEQ ID NO: 1)之編號，SEQ ID NO: 6及SEQ ID NO: 26之肽可在位置16、18、19、24、26或28中之任一者處進一步經Aib取代修飾，或SEQ ID NO: 6之肽視情況在位置12處經醯化Lys取代。

[0085] 在一個實施例中，GLP-1結抗劑肽包含胺基酸序列 $DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}R_{20}$ (SEQ ID NO: 6)或 $DVWRYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}R_{20}$ (SEQ ID NO: 7))，或與SEQ ID NO: 6或SEQ ID NO: 7相差1或2個胺基酸取代的胺基酸序列，其中X_{11}為Trp或dTrp，X_{40}為具有與胺基酸之側鏈連接、大小足夠之醯基以以高親和力結合血清白蛋白的胺基酸，視情況其中醯基經由間隔子連接，且R_{20}為COOH或$CONH_2$，視情況相對於原生艾塞那肽4 (SEQ ID NO: 1)之編號在位置16、18、19、24、26或28中之任一者處經Aib取代，且視情況其中C端胺基酸之羧基經醯胺取代(亦即，R_{20}為$CONH_2$)。在一個實施例中，X_{40}為包含式I (視情況，Lys)、式II (視情況，Ser)或式III (視情況，Cys)之結構的胺基酸，其中式I、II及III中之各者為：



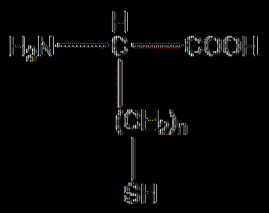
其中n = 1至4

[式II]：



其中n = 1至4

[式II]



其中n = 1至4

[式III]。

[0086] 在一個實施例中，GLP-1指抗劑肽包含以下之胺基酸序列：

DVX$_{11}$RYLEEQAVREFIEWLVRGGPSSGAPPPSX$_{40}$-COOH (SEQ ID NO:9)或

DVX$_{11}$RYLEEQAVREFIEWLVRGGPSSGAPPPSX$_{40}$-NH$_2$ (SEQ ID NO:10)，其中X$_{11}$為Trp或dTrp，且X$_{40}$為醯基與胺基酸之側鏈連接(視情況經由間隔子)之胺基酸。在一個實施例中，X$_{40}$為醯化Lys。

[0087] 根據一個實施例，提供一種GLP-1受體指抗劑肽，其具有以下之胺基酸序列：

DVWX$_{12}$YLEEQAVREFIEWLVRGGPSSGAPPPSX$_{40}$-NH$_2$ (SEQ ID NO: 8)，

其中

X$_{12}$為醯化Lys；及

X$_{40}$為具有醯胺取代C端羧酸之醯化Lys，其中醯化Lys之醯基為C16-C18酸或二酸，其視情況經由間隔子與Lys側鏈連接。

[0088] 在又另一態樣中，本文揭示之任一GLP-1受體指抗劑之位置1處之胺基酸經修飾以抑制該肽之蛋白酶降解。在一個實施例中，藉由

以下來實現蛋白酶之抑制：

i.醯化N端胺基酸之側鏈；

ii. N端胺基酸經其D-立體異構物取代；

iii.修飾N端α胺，包括例如共價連接乙醯基與α胺或移除α胺基；或

iv. i)-iii)之任何組合。

【0089】在一個實施例中，提供一種包含$DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}R_2$ (SEQ ID NO: 6)之序列之肽，其相對於SEQ ID NO: 6具有多達3個胺基酸修飾，其中X_{11}為Trp或dTrp，X_{40}為醯化胺基酸，且R_{20}為COOH或$CONH_2$，其中該肽對於人類GLP-1展現拮抗劑活性。

【0090】在一個實施例中，GLP-1受體拮抗劑包含選自由以下組成之群之肽：

DV(dW)RYLEEQAVREFIEWLVRGGPSSGAPPPSX40 R20，(SEQ ID NO: 27)

DVWRYLEEQAVREFIEWLVRGGPSSGAPPPSX40 R20，(SEQ ID NO: 28)

DV(dW)RYLE(Aib)QAVREFIEWLVRGGPSSGAPPPSX40 R20，(SEQ ID NO: 29)

DVWRYLE(Aib)QAVREFIEWLVRGGPSSGAPPPSX40 R20，(SEQ ID NO: 30)

DV(dW)RYLEEQ(Aib)VREFIEWLVRGGPSSGAPPPSX40 R20，(SEQ ID NO: 31)

DVWRYLEEQ(Aib)VREFIEWLVRGGPSSGAPPPSX40 R20，(SEQ

ID NO: 32)

DV(dW)RYLEEQA(Aib)REFIEWLVRGGPSSGAPPPSX40 R20 ，

(SEQ ID NO: 33)

DVWRYLEEQA(Aib)REFIEWLVRGGPSSGAPPPSX40 R20，(SEQ ID NO: 34)

DV(dW)RYLEEQAVREFI(Aib)WLVRGGPSSGAPPPSX40 R20 ，

(SEQ ID NO: 35)

DVWRYLEEQAVREFI(Aib)WLVRGGPSSGAPPPSX40 R20，(SEQ ID NO: 36)

DV(dW)RYLEEQAVREFIEW(Aib)VRGGPSSGAPPPSX40 R20 ，

(SEQ ID NO: 37)

DVWRYLEEQAVREFIEW(Aib)VRGGPSSGAPPPSX40 R20，(SEQ ID NO: 38)

DV(dW)RYLEEQAVREFIEWLV(Aib)GGPSSGAPPPSX40 R20 ，

(SEQ ID NO: 39)

DVWRYLEEQAVREFIEWLV(Aib)GGPSSGAPPPSX40 R20，(SEQ ID NO: 40)

DV(dW)RYLEEQAV(dR)EFIEWLVRGGPSSGAPPPSX40 R20 ，

(SEQ ID NO: 41)

DVWRYLEEQAV(dR)EFIEWLVRGGPSSGAPPPSX$_{40}$ R$_{20}$ ，(SEQ ID NO: 42)，

其中X$_{40}$為醯化胺基酸，視情況為經C16-C18脂肪酸或二酸醯化之Lys，且R$_{20}$為COOH或CONH$_2$，其中肽對於人類GLP-1展現拮抗劑活性。

【0091】在一個實施例中，GLP-1受體拮抗劑包含選自由以下組成之群之肽：

R_{10}-DV(dW)RYLEEQAVREFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 100)

R_{10}-DVWRYLEEQAVREFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 101)

R_{10}-DV(dW)RYLE(Aib)QAVREFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 102)

R_{10}-DVWRYLE(Aib)QAVREFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 103)

R_{10}-DV(dW)RYLEEQ(Aib)VREFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 104)

R_{10}-DVWRYLEEQ(Aib)VREFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 105)

R_{10}-DV(dW)RYLEEQA(Aib)REFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 106)

R_{10}-DVWRYLEEQA(Aib)REFIEWLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 107)

R_{10}-DV(dW)RYLEEQAVREFI(Aib)WLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 108)

R_{10}-DVWRYLEEQAVREFI(Aib)WLVRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 109)

R_{10}-DV(dW)RYLEEQAVREFIEW(Aib)VRGGPSSGAPPPS-R_{20}，

(SEQ ID NO: 110)

R_{10}-DVWRYLEEQAVREFIEW(Aib)VRGGPSSGAPPPS-R_{20}，(SEQ ID NO: 111)

R_{10}-DV(dW)RYLEEQAVREFIEWLV(Aib)GGPSSGAPPPS-R_{20} ，(SEQ ID NO: 112)

R_{10} DVWRYLEEQAVREFIEWLV(Aib)GGPSSGAPPPS-R_{20}，(SEQ ID NO: 113)

R_{10}-DV(dW)RYLEEQAV(dR)EFIEWLVRGGPSSGAPPPS-R_{20} ，(SEQ ID NO: 114)

R_{10}-DVWRYLEEQAV(dR)EFIEWLVRGGPSSGAPPPS-R_{20} ，(SEQ ID NO: 115)，

其中R_{10}為與多肽之N端α胺連接之-$CO(CH_2)_{14-20}CH_3$或-$CO(CH_2)_{14-20}COOH$，且R_{20}為COOH或$CONH_2$，其中肽對於人類GLP-1展現拮抗劑活性。

【0092】 本發明之額外例示物種包括表1中列舉之彼等物種：

表1

SEQ ID NO.	描述/化合物註冊	序列
1	艾塞那肽-4	HGEGTFTSDVSKQMEEEAVRLFIEWLKNGGPSSGAPPPS
2	Ex-4 (9-39)a	DVSKQMEEEAVRLFIEWLKNGGPSSGAPPPS
3	Jant4 9-40am; K40[C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPS**K[C16]**-OH
4		DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK
5		$DX_{10}X_{11}RYLX_{15}X_{16}QAVREFX_{23}EWLVRGGPSSGAPPPSX_{40}$
6		$DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}$
7		$DVWRYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}$
8		$DVWX_{12}YLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}$-$NH_2$)
9		$DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}$-COOH
10		$DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40}$-$NH_2$
11		$DVX_{11}RYLX_{15}X_{16}QAVREFX_{23}EWLVRGGPSSGAPPPSK$
12		$DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSX_{40}$

13		DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSX$_{40}$
14	X$_7$X$_8$ = dK(mPeg-γE-二酸C18)(N-Me-Gly)	X$_7$X$_8$DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSX$_{40}$
15	X$_7$X$_8$ = dK(mPeg-γE-二酸C18)(N-iPr-Gly	X$_7$X$_8$DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSX$_{40}$
16	9-40AC; Jant4 (R12,E24,R28) K40[mPEG-gE-C16]	DVS**R**YLEEQAVREFI**E**WLV**R**GGPSSGAPPPS**K[miniPEG-γE-C16]**-OH
17	9-40AC, dK7(mPeg-γE(二酸C18))G8 R12,E24,R28, K40(mPeg-γE(C16)) (前藥)	**dK(mPeg-γE-DiAcidC18)G**DVS**R**YLEEQAVREFI**E**WLV**R**GGPSSGAPPPS**K[miniPEG-gE-C16]**-OH
18	9-40AC, dK7(mPeg-γE(二酸C18)) (N-iPr-Gly8) R12,E24,R28, K40(mPeg-γE(C16)) (前藥)	**dK(mPeg-γE-DiAcidC18)(N-iPr-Gly)**DVS**R**YLEEQAVREFI**E**WLV**R**GGPSSGAPPPSK**[miniPEG-gE-C16]-OH**
19	9-40AC, dK7(mPeg-γE(二酸C18)) (N-Me-Gly8) R12,E24,R28, K40(mPeg-γE(C16)) (前藥)	dK(mPeg-γE-DiAcidC18)(N-Me-Gly8)DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK[miniPEG-gE-C16]-OH
20	Jant9-40am, dK7(C18二酸-gE-mPeg-K(mPeg-gE-C18二酸),G8, K40(mPeg-gE-C18二酸)	dK7(C18二酸-gE-mPeg-K(mPeg-gE-C18二酸)GDVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK[miniPEG-gE-C18二酸)-NH2
21	Jant9-40am, dK7(C18二酸-gE-mPeg-K(mPeg-gE-C18二酸),G8, K40(mPeg-gE-C16)	dK7(C18二酸-gE-mPeg-K(mPeg-gE- C18二酸)GDVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK[miniPEG-gE-C16)-NH2

22	Jant9-40am, dK7(C18二酸-gE-mPeg-K(mPeg-gE-C18二酸),N-meGly, K40(mPeg-gE-C16)	dK7(C18二酸-gE-mPeg-K(mPeg-gE-C18二酸)-N-MeGly-DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK[miniPEG-gE-C16)-NH2
23		DV$X_{11}X_{12}$YL$X_{15}X_{16}$QA$X_{19}X_{20}$EFX_{23}EWLVRGGPSSGAPPPSX_{40}
24		DV$X_{11}X_{12}$YLEX_{16}QAVREFIEWLVRGGPSSGAPPPSX_{40}
25		DVX_{11}RYLQ$X_{15}X_{16}$AVREFX_{23}EWLVRGGPSSGAPPPSX_{40}
26		X_7X_8DVX_{11}RYLEEQAVREFIEWLVRGGPSSGAPPPS$X_{40}R_{20}$
27		DV(dW)RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40} R_{20}
28		DVWRYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40} R_{20}
29		DV(dW)RYLE(Aib)QAVREFIEWLVRGGPSSGAPPPSX_{40} R_{20}
30		DVWRYLE(Aib)QAVREFIEWLVRGGPSSGAPPPSX_{40} R_{20}
31		DV(dW)RYLEEQ(Aib)VREFIEWLVRGGPSSGAPPPSX_{40} R_{20}
32		DVWRYLEEQ(Aib)VREFIEWLVRGGPSSGAPPPSX_{40} R_{20}
33		DV(dW)RYLEEQA(Aib)REFIEWLVRGGPSSGAPPPSX_{40} R_{20}
34		DVWRYLEEQA(Aib)REFIEWLVRGGPSSGAPPPSX_{40} R_{20}
35		DV(dW)RYLEEQAVREFI(Aib)WLVRGGPSSGAPPPSX_{40} R_{20}
36		DVWRYLEEQAVREFI(Aib)WLVRGGPSSGAPPPSX_{40} R_{20}
37		DV(dW)RYLEEQAVREFIEW(Aib)VRGGPSSGAPPPSX_{40} R_{20}
38		DVWRYLEEQAVREFIEW(Aib)VRGGPSSGAPPPSX_{40} R_{20}
39		DV(dW)RYLEEQAVREFIEWLV(Aib)GGPSSGAPPPSX_{40} R_{20}
40		DVWRYLEEQAVREFIEWLV(Aib)GGPSSGAPPPSX_{40} R_{20}
41		DV(dW)RYLEEQAV(dR)EFIEWLVRGGPSSGAPPPSX_{40} R_{20}
42		DVWRYLEEQAV(dR)EFIEWLVRGGPSSGAPPPSX_{40} R_{20}
43	9-40am; Jant4 (K27, Aib28) K40[C16]	DVSSYLEEQAVREFIAWLK(Aib)GGPSSGAPPPSK[C16]-NH2
44	9-40am; Jant4 (Aib26) K40[C16]	DVSSYLEEQAVREFIAW(Aib)VKGGPSSGAPPPSK[C16]-NH2
45	9-40am; Jant4 (Aib19) K40[C16]	DVSSYLEEQA(Aib)REFIAWLVKGGPSSGAPPPSK[C16]-NH2
46	9-40am; Jant4 (Aib18) K40[C16]	DVSSYLEEQ(Aib)VREFIAWLVKGGPSSGAPPPSK[C16]-NH2
47	9-40am; Jant4 K40[C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[C16]-NH2
48	9-40am; Jant4 K40[(mPEG)2-gE-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[(miniPEG)2-gE-C16]-NH2
49	9-40am; Jant4 (dE15) K40[C16]	DVSSYL(dE)EQAVREFIAWLVKGGPSSGAPPPSK[C16]-NH2
50	9-40am; Jant4 (dV19) K40[C16]	DVSSYLEEQA(dV)REFIAWLVKGGPSSGAPPPSK[C16]-NH2

51	9-40am; Jant4 (dI23) K40[C16]	DVSSYLEEQAVREF(dI)AWLVKGGPSSGAPPPSK[C16]-NH2
52	9-40am; Jant4 K40[gE-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE-C16]-NH2
53	9-40am; Jant4 K40[gE2-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE2-C16]-NH2
54	9-40am; Jant4 K40[gE4-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE4-C16]-NH2
55	9-40am; Jant4 K40[gE6-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE6-C16]-NH2
56	9-40am; Jant4 K40[mPEG-gE-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[miniPEG-gE-C16]-NH2
57	9-40am; Jant4 K40[EP2E-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE-(miniPEG)2-gE-C16]-NH2
58	9-40am; Jant4 K40(P2E2-C16)	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[(miniPEG)2-gE2-C16]-NH2
59	9-40am; Jant4 K40(PEPE-C16)	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[miniPEG-gE-miniPEG-gE-C16]-NH2
60	9-40am; Jant4 K40[PE2P-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[miniPEG-gE2-miniPEG-C16]-NH2
61	9-40am; Jant4 K40[E2P2-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE2-(miniPEG)2-C16]-NH2
62	9-40am; Jant4 K40[EPEP-C16]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE-miniPEG-gE-miniPEG-C16]-NH2
63	9-40am;Jant4 K40[DiAcC18]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[二酸C18]-NH2
64	9-40am; Jant4 K40[gE2-DiAcC18]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE2-二酸C18]-NH2
65	9-40am; Jant4 K40[gE4-DiAcC18]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE4-二酸C18]-NH2
66	9-40am; Jant4 K40[gE6-DiAcC18]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[gE6-二酸C18]-NH2
67	9-40am; Jant4 K40[(mPEG)2-gE-DiAC18]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[(miniPEG)2-gE-二酸C18]-NH2
68	9-40am; Jant4 K40[mPEG-gE-DiAcC18]	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK[miniPEG-gE-DiAcC18]-NH2
69	9-40am; Jant4 (R28) K40[C16]	DVSSYLEEQAVREFIAWLVRGGPSSGAPPPSK[C16]-NH2

70	9-40am; Jant4 (E24,R28) K40[C16]	DVSSYLEEQAVREFIEWLVRGGPSSGAPPPSK[C16]-NH2
71	9-40am; Jant4 (E17,R28) K40[C16]	DVSSYLEEEAVREFIAWLVRGGPSSGAPPPSK[C16]-NH2
72	9-40am; Jant4 (E17,E24,R28) K40[C16]	DVSSYLEEEAVREFIEWLVRGGPSSGAPPPSK[C16]-NH2
73	9-40am; Jant4 (R12,R28) K40[C16]	DVSRYLEEQAVREFIAWLVRGGPSSGAPPPSK[C16]-NH2
74	9-40am; Jant4 (R12,E24,R28) K40[C16]	DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSK[C16]-NH2
75	9-40am; Jant4 (R12,E17,E24,R28) K40[C16]	DVSRYLEEEAVREFIEWLVRGGPSSGAPPPSK[C16]-NH2
76	Ex9 K40[C16]	DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSK[C16]-NH2
77	9-40AC; Jant4 (R28) K40[mPEG-gE-C16]	DVSSYLEEQAVREFIAWLVRGGPSSGAPPPSK[miniPEG-gE-C16]-OH
78	9-40AC; Jant4 (E24,R28) K40[mPEG-gE-C16]	DVSSYLEEQAVREFIEWLVRGGPSSGAPPPSK[miniPEG-gE-C16]-OH
79	9-40AC; Jant4 (E24,R27,V28) K40[mPEG-gE-C16]	DVSSYLEEQAVREFIEWLRVGGPSSGAPPPSK[miniPEG-gE-C16]-OH
80	9-40AC; Jant4 (E24,R27,Aib28) K40[mPEG-gE-C16]	DVSSYLEEQAVREFIEWLR(Aib)GGPSSGAPPPSK[miniPEG-gE-C16]-OH
81	9-40am; Jant4 (Aib27) K40[C16]	DVSSYLEEQAVREFIAWL(Aib)KGGPSSGAPPPSK[C16]-NH2
82	9-40am; Jant4 (K26, Aib28) K40[C16]	DVSSYLEEQAVREFIAWKV(Aib)GGPSSGAPPPSK[C16]-NH2
83	9-40am; Jant4 (Aib24) K40[C16]	DVSSYLEEQAVREFI(Aib)WLVKGGPSSGAPPPSK[C16]-NH2
84	9-40am; Jant4 (Aib16) K40[C16]	DVSSYLE(Aib)QAVREFIAWLVKGGPSSGAPPPSK[C16]-NH2
85	9-40am; Jant4 (dE16) K40[C16]	DVSSYLE(dE)QAVREFIAWLVKGGPSSGAPPPSK[C16]-NH2
86	9-40am; Jant4 (dQ17) K40[C16]	DVSSYLEE(dQ)AVREFIAWLVKGGPSSGAPPPSK[C16]-NH2

87	9-40am; Jant4 (dR20) K40[C16]	DVSSYLEEQAV(dR)EFIAWLVKGGPSSGAPPPSK[C16]-NH2
88	9-40am; Jant4 (dE21) K40[C16]	DVSSYLEEQAVR(dE)FIAWLVKGGPSSGAPPPSK[C16]-NH2
89	Ex9, dK7(PEG2-γE(C16)), G8	dK(Peg2-gE(C16)) GDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH2
90	Ex9-40am, K40(C18 二酸)	DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSK(C18 二酸)-NH2
91	Ex9-40am, W11, K40(C18二酸)	DLWKQMEEEAVRLFIEWLKNGGPSSGAPPPSK(C18 二酸)-NH2
92	Ex9-40am, dW11, K40(C18二酸)	DLdWKQMEEEAVRLFIEWLKNGGPSSGAPPPSK(C18 二酸)-NH2
93	Ex9-40am, W11, K40(mPeg-gE-C18 二酸)	DLWKQMEEEAVRLFIEWLKNGGPSSGAPPPSK(mPeg-gE(C18二酸))-NH2
94	Ex9-40am, dW11,K40(mPeg-gE-C18二酸)	DLdWKQMEEEAVRLFIEWLKNGGPSSGAPPPSK(mPeg-gE(C18二酸))-NH2
95	9-40am; Jant4 K40	DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK-NH2

【0093】 在一個實施例中，製備包含兩種或更多種本發明之GLP-1受體拮抗劑肽之二聚體及多聚體，包括同多聚體或異多聚體、或同二聚體或異二聚體。兩種或更多種GLP-1受體拮抗劑肽可使用熟習此項技術者已知之標準連接劑及程序連接在一起。舉例而言，經由使用雙官能硫醇交聯劑及雙官能胺交聯劑，可在兩個肽之間形成二聚體，尤其對於包含半胱胺酸、離胺酸、鳥胺酸、高半胱胺酸或乙醯基苯丙胺酸殘基或經其取代的GLP-1受體拮抗劑肽。二聚體可為同二聚體，或者可為異二聚體。在例示性實施例中，連接兩種(或更多種)類似物之連接子為PEG，例如5 kDa PEG、20 kDa PEG。在一些實施例中，連接子為二硫鍵。舉例而言，二聚體之各單體可包含Cys殘基(例如定位於末端或內部之Cys)且各Cys殘基之硫原子參與二硫鍵之形成。在例示性態樣中，二聚體之各單體係經由硫醚鍵連接。在例示性態樣中，一個單體之Lys殘基之ε胺鍵合至Cys殘基，其轉而經由化學部分與另一單體之Lys殘基之ε胺連接。

【0094】 在一些實施例中，單體係經由末端胺基酸(例如N端或C端，視情況其中胺基酸添加至待二聚之肽之末端)、經由內部胺基酸、或經由至少一個單體之末端胺基酸及至少一個另一單體之內部胺基酸來連接。在一些實施例中，多聚體之單體以「尾-至-尾」取向連接在一起，其中各單體之C端胺基酸連接在一起。或者，在一個實施例中，多聚體以「頭部-至-頭部」取向連接在一起，其中各單體之N端胺基酸連接在一起。

【0095】 在一個實施例中，本文揭示之任一GLP-1拮抗劑肽之C端胺基酸可經修飾以用醯胺置換原生羧基。在一個實施例中，本文揭示之任一GLP-1拮抗劑肽之C端胺基酸包含原生胺基酸羧基。

【0096】

醫藥組合物

本發明進一步提供包含本發明之GLP-1受體拮抗劑肽、二聚體、多聚體或結合物中之任一者(或其組合)及醫藥學上可接受之載劑、稀釋劑或賦形劑的醫藥組合物。醫藥組合物較佳地為無菌的且適合於非經腸投與。

【0097】 根據一個實施例，提供一種醫藥組合物，其包含：本文揭示之任一新穎GLP-1受體拮抗劑，較佳地在至少90%、91%、92%、93%、94%、95%、96%、97%、98%或99%之純度水平；及醫藥學上可接受之稀釋劑、載劑或賦形劑。此類組合物可含有濃度為至少0.1-10 mg/ml或更高之如本文所揭示的GLP-1受體拮抗劑。在一個實施例中，醫藥組合物包含經滅菌且視情況儲存在各種封裝容器內之水溶液。在其他實施例中，醫藥組合物包含凍乾粉末。醫藥組合物可進一步封裝為包括用於向患者投與組合物之拋棄式裝置之套組的一部分。容器或套組可針對儲存

在環境室溫下或冷藏溫度下進行標記。在一個實施例中，醫藥組合物及/或套組包含本文揭示之任一GLP-1受體拮抗劑以及適用於治療低血糖症之任何現有療法，包括但不限於葡萄糖補充劑(例如右旋糖)；葡萄糖升高劑，諸如升糖素及升糖素類似物以及胰島素分泌抑制劑(例如二氮嗪、奧曲肽)。

【0098】 根據一個實施例，考慮本文所揭示之醫藥組合物用於治療或預防低血糖症病狀之方法，且更具體言之治療或預防非典型低血糖症或與低血糖症相關之醫學病狀。

【0099】 本發明之組合物可使用任何標準投與途徑投與。適合於非經腸投與之調配物包括可含有抗氧化劑、緩衝劑、抑菌劑及使調配物與預期接受者血液等張之溶質的水性及非水性無菌注射溶液；及可包括懸浮劑、增溶劑、增稠劑、穩定劑及防腐劑之水性及非水性無菌懸浮液。術語「非經腸」意謂不經消化道，而藉由一些其他途徑，諸如皮下、肌肉內、脊柱內或靜脈內。在一個實施例中，包含本發明之GLP-1受體拮抗劑之醫藥組合物經調配用於皮下投與或靜脈內投與。在一個實施例中，本發明之GLP-1受體拮抗劑，單獨或與其他合適組分組合，可製備為待經由吸入投與之氣溶膠調配物形式。

【0100】 在一個實施例中，組合物經調配用於藉由將本發明之GLP-1受體拮抗劑與可充分強化肽拮抗劑之吸收的吸收增強劑共調配來經口遞送。N-[8-(2-羥苯甲醯基)胺基]辛酸鈉(SNAC)為已據報導增強多種多樣的分子(包括肽(諸如胰島素)、GLP-1、降鈣素及其他大分子(諸如肝素))之滲透性的遞送劑。根據一個實施例，提供醫藥組合物用於經口遞送，其中組合物包含本發明之GLP-1受體拮抗劑及SNAC，視情況其中醫藥組合物

經調配為錠劑形式。

【0101】

醯化

根據一個實施例，本文揭示之展現GLP-1拮抗劑活性之肽、二聚體或多聚體中之任一者可進一步經修飾以在向溫血哺乳動物(包含例如智人(*homo sapiens*))投與時具有改善的治療指數及活體內延長作用時間。更特定言之，在一個實施例中，本文所揭示之肽及二聚體藉由將烷基或醯基與拮抗劑肽之胺基酸(視情況為離胺酸、絲胺酸或半胱胺酸)之側鏈共價連接來進行修飾，其中烷基或醯基具有足夠大小以以高親和力結合血清白蛋白。在一個實施例中，烷基化或醯化胺基酸位於GLP-1拮抗劑肽或二聚體之C端。在一個實施例中，GLP-1拮抗劑肽包含兩個醯化胺基酸。在一個實施例中，GLP-1受體拮抗劑肽之胺基酸中之一或多者經脂肪酸或脂肪二酸醯化，視情況經C16-C18脂肪酸或C16-C18脂肪二酸醯化。根據一個實施例，本文揭示之GLP-1拮抗劑肽或二聚體之一或多個離胺酸殘基藉由將C16-C18脂肪酸或C16-C18脂肪二酸與離胺酸之側鏈共價鍵聯(視情況經由間隔子)進行修飾。在一個實施例中，醯化離胺酸殘基為GLP-1拮抗劑肽之C端胺基酸。在一個實施例中，醯化胺基酸存在於GLP-1拮抗劑肽之位置40處及選自位置7或12之第二位置處。在具有兩個或更多個醯化胺基酸之實施例中，醯化胺基酸可相同或不同，且連接的醯基可相同或不同，其限制條件為醯基具有足夠大小以結合血清白蛋白。在一個實施例中，醯化胺基酸為離胺酸，其中側鏈視情況經由間隔子與C16-C18脂肪酸或C16-C18脂肪二酸連接。

【0102】 在一個實施例中，C16-C18脂肪酸或C16-C18脂肪二酸經

由間隔子與胺基酸之側鏈連接，其中間隔子包含miniPEG、γGlu、或miniPEG及/或γGlu之任何多聚體或組合。在一個實施例中，本文揭示之任一GLP-1受體拮抗劑肽可經修飾以參考艾塞那肽4之原生序列視情況在選自7、12及40位置處包含醯化胺基酸。在一個實施例中，醯化胺基酸為C16至C18脂肪酸或C16至C18脂肪二酸經由包含以下結構之間隔子與離胺酸側鏈連接的離胺酸殘基：

-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-

其中k為選自2、4、6或8之整數，且p及q獨立地為選自1或2之整數。在一個實施例中，間隔子選自由以下組成之群：

-(γ麩胺酸)-[$COCH_2(OCH_2CH_2)_kNH]_2$-(γ麩胺酸)-，或

-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-，或

-[$COCH_2(OCH_2CH_2)_kNH]_2$-(γ麩胺酸)$_2$-，或

-[$COCH_2(OCH_2CH_2)_kNH$]-(γ麩胺酸)$_2$-[$COCH_2(OCH_2CH_2)_kNH$]-，或

-(γ麩胺酸)$_2$-[$COCH_2(OCH_2CH_2)_kNH]_2$，或

-(γ麩胺酸)-[$COCH_2(OCH_2CH_2)_kNH$]-(γ麩胺酸)$_p$-[$COCH_2(OCH_2CH_2)_kNH$]-、或γ麩胺酸、或γ麩胺酸-γ麩胺酸二肽、或γ麩胺酸-[$COCH_2(OCH_2CH_2)_kNH$]-γ麩胺酸，其中

k為選自1-8之範圍之整數；及

q及p獨立地為選自1-8之範圍之整數，視情況其中k為2且q及p獨立地為1或2。在一個實施例中，間隔子為

-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-，其中

k為選自1-4之範圍之整數；及

q及p獨立地為選自1-4之範圍之整數，視情況其中k為2且q及p獨立地為1或2，視情況其中k為2且q及p均為1。

【0103】 在一個實施例中，GLP-1受體拮抗劑肽包含視情況位於肽之C端處之醯化Lys，其中Lys之側鏈經C16-C18二酸醯化，其經由包含結構：-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-之間隔子，其中

k為選自1-4之範圍之整數；及

q及p獨立地為選自1-4之範圍之整數，視情況其中k為2且q及p獨立地為1或2，視情況其中k為2且q及p均為1。在一個實施例中，醯化Lys之側鏈包含結構-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-$COC_{16}H_{32}CO_2H$，其中k為2且p及q獨立地為1或2。在一個實施例中，提供一種GLP-1受體拮抗劑，其包含序列DV(dW)RYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40} R_{20} (SEQ ID NO: 27)或DVWRYLEEQAVREFIEWLVRGGPSSGAPPPSX_{40} R_{20} (SEQ ID NO: 28)，其中

R_{20}為COOH或$CONH_2$，且X_{40}為經-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-$COC_{14}H_{28}CO_2H$ 或 -[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-$COC_{16}H_{32}CO_2H$醯化之Lys，其中k為2且p及q獨立地為1或2。

【0104】

結合物

在一些實施例中，本文所揭示之任一GLP-1拮抗劑肽與免疫球蛋白或其部分(例如可變區、CDR或Fc區)結合。免疫球蛋白(Ig)之已知類型包含IgG、IgA、IgE、IgD或IgM。Fc區為Ig重鏈之C端區，其負責與進行活性之Fc受體結合，該等活性諸如再循環(其導致半衰期延長)、抗體依賴性

細胞介導之細胞毒性(ADCC)及補體依賴性細胞毒性(CDC)。

【0105】 在一些實施例中，本文所揭示之任一GLP-1拮抗劑肽與親水性部分結合。親水性部分可在任何適合用於使蛋白質與活化聚合物分子反應之條件下與GLP-1拮抗劑肽共價連接。可用於將水溶性聚合物與一或多種蛋白質連接之活化性基團包括但不限於碸、順丁烯二醯亞胺、硫氫基、硫醇、三氟甲磺酸鹽、三氟乙磺酸鹽、氮雜環丙烷、環氧乙烷、5-吡啶基及α-鹵代醯基(例如α-碘乙酸、α-溴乙酸、α-氯乙酸)。若藉由還原性烷基化與肽連接，則所選聚合物應具有單一反應性醛以使得控制聚合度。參見例如Kinstler等人, *Adv. Drug. Delivery Rev.* 54: 477-485 (2002)；Roberts等人, *Adv. Drug Delivery Rev*. 54: 459-476 (2002)；及Zalipsky等人, *Adv. Drug Delivery Rev.* 16: 157-182 (1995)。

【0106】 合適的親水性部分包括聚乙二醇(PEG)、聚丙二醇、聚氧乙烯化多元醇(例如POG)、聚氧乙烯化山梨糖醇、聚氧乙烯化葡萄糖、聚氧乙烯化甘油(POG)、聚環氧烷、聚乙二醇丙醛、乙二醇/丙二醇之共聚物、單甲氧基-聚乙二醇、單-(C1-C10)烷氧基-或芳氧基-聚乙二醇、羧甲基纖維素、聚縮醛、聚乙烯醇(PVA)、聚乙烯吡咯啶酮、聚-1,3-二氧雜環戊烷、聚-1,3,6-三噁烷、乙烯/順丁烯二酸酐共聚物、聚(β-胺基酸) (均聚物或無規共聚物二者中之一者)、聚(n-乙烯吡咯啶酮)聚乙二醇、聚丙二醇均聚物(PPG)及其他聚環氧烷、聚環氧丙烷/環氧乙烷共聚物、結腸酸或其他多醣聚合物、Ficoll或聚葡萄糖及其混合物。聚葡萄糖為主要由α1-6鍵聯連接之葡萄糖次單元的多醣聚合物。可獲得在多個分子量範圍內之聚葡萄糖，例如約1 kD至約100 kD，或約5 kD、10 kD、15 kD或20 kD至約20 kD、30 kD、40 kD、50 kD、60 kD、70 kD、80 kD或90 kD。在一個實

施例中，親水性部分(例如聚乙二醇鏈)具有選自約500至約40,000道爾頓之範圍的分子量。在一些實施例中，親水性部分為具有選自約500至約5,000道爾頓、或約1,000至約5,000道爾頓之範圍的分子量之聚乙二醇鏈。在另一實施例中，親水性部分(例如聚乙二醇鏈)具有約10,000至約20,000道爾頓之分子量。

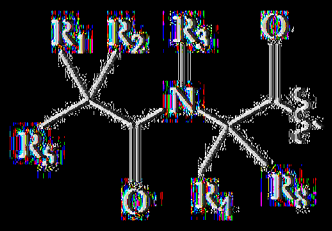
【0107】 在一個實施例中，提供一種SEQ ID NO: 5或SEQ ID NO: 23之肽之結合物衍生物，其中二肽經由肽鍵與SEQ ID NO: 5或SEQ ID NO: 23之肽之N端共價連接，視情況其中二肽之一個胺基酸為醯化胺基酸。在一個實施例中，二肽具有X_7X_8之結構，其中X_7為醯化胺基酸且X_8為任何胺基酸，視情況其中X_7為醯化Lys或dLys且X_8為Gly或C_1-C_4 N-烷基化Gly，視情況其中X_7為經C14-C20脂肪酸或脂肪二酸醯化之Lys或dLys且X_8為Gly或C_1-C_4 N-烷基化Gly (視情況為Gly或肌胺酸)，視情況其中X_7為經由本文所揭示之任一間隔子經C14-C20脂肪酸或脂肪二酸醯化的Lys且X_8為C_1-C_4 N-烷基化Gly (視情況為Gly或肌胺酸)。

【0108】 根據一個實施例，提供一種GLP-1受體拮抗劑肽中之任一者之結合物衍生物，其中自裂解二肽經由醯胺鍵與本文所揭示之GLP-1拮抗劑肽之胺基酸側鏈胺或N端α胺共價結合。在一個實施例中，自裂解二肽與GLP-1拮抗劑肽之N端α胺共價結合。

【0109】 在例示性態樣中，自裂解二肽包含結構：A-B，其中A為胺基酸或羥基酸；及B為經由A-B與GLP-1拮抗劑肽之胺之間的醯胺鍵與GLP-1拮抗劑肽連接之N-烷基化胺基酸，視情況其中在生理條件下，在PBS中，A-B自GLP-1拮抗劑肽之化學裂解半衰期(t1/2)為至少約1小時至約1週。如本文所用，術語「羥基酸」係指已經修飾以用羥基置換α碳胺基

之胺基酸。

[0110] 在一些實施例中，自裂解二肽具有以下通式結構：



其中

R_1、R_2、R_4及R_8獨立地選自由以下組成之群：H、C_1-C_{18}烷基、C_2-C_{18}烯基、(C_1-C_{18}烷基)OH、(C_1-C_{18}烷基)SH、(C_2-C_3烷基)SCH_3、(C_1-C_4烷基)$CONH_2$、(C_1-C_4烷基)COOH、(C_1-C_4烷基)NH_2、(C_1-C_4烷基)$NHC(NH_{2+1})NH_2$、(C_0-C_4烷基)(C_3-C_6環烷基)、(C_0-C_4烷基)(C_2-C_5雜環)、(C_0-C_4烷基)(C_6-C_{10}芳基)R_7、(C_1-C_4烷基)(C_3-C_9雜芳基)及C_1-C_{12}烷基(W1)C_1-C_{12}烷基，其中W1為選自由N、S及O組成之群的雜原子；

R_3選自由以下組成之群：C_1-C_{18}烷基、(C_1-C_{18}烷基)OH、(C_1-C_{18}烷基)NH_2、(C_1-C_{18}烷基)SH、(C_0-C_4烷基)(C_3-C_6)環烷基、(C_0-C_4烷基)(C_2-C_5雜環)、(C_0-C_4烷基)(C_6-C_{10}芳基)R_7及(C_1-C_4烷基)(C_3-C_9雜芳基)，或R_4及R_3與其所連接之原子一起形成吡咯啶環；

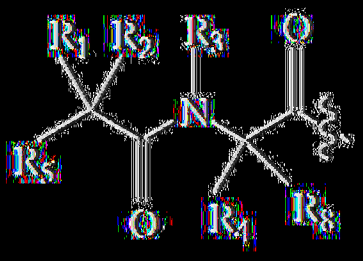
R_5為NHR_6或OH；

R_6為H、C_1-C_8烷基；及

R_7選自由H及OH組成之群，

其中在生理條件下在PBS中，A-B自該GLP-1拮抗劑之化學裂解半衰期($t_{1/2}$)為至少約1小時至約1週。在一個實施例中，二肽A-B與GLP-1拮抗劑胺基酸序列之N端α胺共價連接。

[0111] 在一個實施例中，自裂解二肽具有以下之通式結構：



其中

R_1及R_8獨立地為H或C_1-C_8烷基；

R_2及R_4獨立地選自由以下組成之群：H、C_1-C_8烷基、(C_1-C_4烷基)OH、(C_1-C_4烷基)SH、(C_2-C_3烷基)SCH_3、(C_1-C_4烷基)$CONH_2$、(C_1-C_4烷基)COOH、(C_1-C_4烷基)NH_2及(C_1-C_4烷基)(C_6芳基)R_7；

R_3為C_1-C_6烷基；

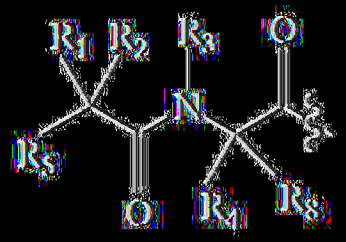
R_5為NH_2；及

R_7選自由氫及OH組成之群。

[0112] 根據一個實施例，本文所揭示之GLP-1抗抗劑肽及二聚體中之任一者可進一步藉由與白裂解二肽鍵聯進行修飾，其中二肽之胺基酸用具有足夠大小以以高親和力結合血清白蛋白之脂肪醯基醯化。

[0113] 在一個實施例中，白裂解二肽「A-B」之胺基酸「A」為經C16-C30脂肪酸或C16-C30二酸醯化之離胺酸殘基。在一個實施例中，A及B經選擇以提供在生理條件下在標準PBS溶液中如下之A-B白本文所揭示之GLP-1抗抗劑肽或二聚體之化學裂解半衰期(t1/2)：至少約24小時至約240小時、約48小時至約168小時、或約48至約120小時、或約70至約100小時。

[0114] 在一個實施例中，白裂解二肽具有以下之通式結構：



其中

R_1包含選自由以下組成之群的側鏈：C_1-C_8烷基、(C_1-C_4烷基)OH、(C_1-C_4烷基)SH、(C_1-C_4烷基)COOH及(C_1-C_4烷基)NH_2，視情況其中C16-C18脂肪酸或C16-C18二酸視情況經由本文所揭示之任一間隔子與該側鏈共價連接，包括選自由以下組成之群的間隔子：γ麩胺酸、γ麩胺酸-γ麩胺酸二肽、-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$及γ麩胺酸-[$COCH_2(OCH_2CH_2)_kNH]_q$-γ麩胺酸，其中

k為選自1-8之範圍之整數；及

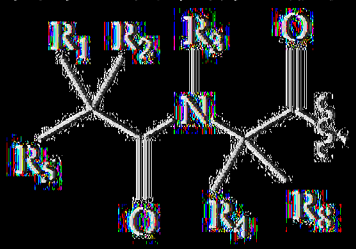
q及p獨立地為選自1-8之範圍之整數，視情況其中k為2且q及p獨立地為1或2；

R_2、R_4及R_8獨立地為H或C_1-C_4烷基；

R_3為C_1-C_6烷基；及

R_5為NH_2。

[0115] 在一個實施例中，自裂解二肽具有以下之通式結構：



其中

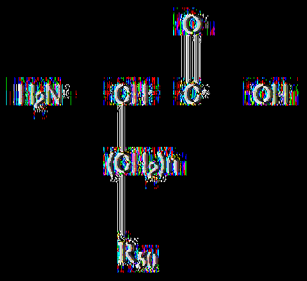
R_1為H、C_1-C_4烷基、(C_1-C_4烷基)OH或(C_1-C_4烷基)NH_2；R_2為H，

R_3為C_1-C_4烷基；

R_4為H或C_1-C_4烷基；R_5為NH_2；及

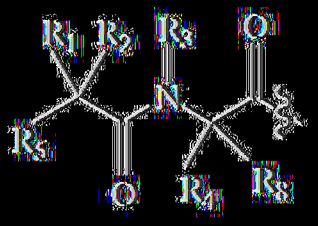
R_8為氫。

[0116] 根據一個實施例，自裂解二肽A-B包含醯化胺基酸殘基作為「A」及N-烷基化Gly殘基作為「B」，其中「B」胺基酸經由醯胺鍵與GLP-1受體拮抗劑肽之N端α胺連接，視情況其中該Lys殘基呈D-構形。在一個實施例中，A-B二肽之醯化胺基酸「A」為具有以下之通式結構之胺基酸：



其中n為選自1-4之範圍之整數，且R_{50}選自由以下組成之群：NH-$CO(CH_2)_{14-20}COOH$、NH-[間隔子]-$CO(CH_2)_{14-20}COOH$、$S(CH_2)_{14-20}COOH$及S-[間隔子]-$CO(CH_2)_{14-20}COOH$，其中[間隔子]為本文所揭示之任一間隔子。在一個實施例中，A之醯化胺基酸獨立地選自離胺酸、d-離胺酸、鳥胺酸、半胱胺酸或高半胱胺酸，其中該醯化胺基酸之側鏈視情況經由包含胺基酸或二肽之間隔子與C16-C22脂肪酸或C16-C22二酸共價連接。在一個實施例中，間隔子包含γ麩胺酸。在一個實施例中，間隔子包含呈任何組合之多個γ麩胺酸單元及miniPEG聚合物。在一個實施例中，視情況選用之間隔子包含兩個γ麩胺酸，視情況其中該兩個γ麩胺酸經由間插自胺化miniPEG聚合物$[COCH_2(OCH_2CH_2)_kNH]_q$彼此接合，其中k及q各自為獨立地選自1、2、3、4、5、6、7、或8之整數。

[0117] 在一個實施例中，自裂解二肽具有以下之通式結構：



其中

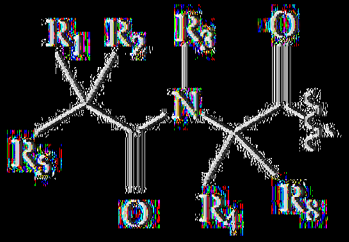
R_1為(C_4烷基)NH_2或(C_4烷基)NH(mPeg-γE-二酸)-C18；

R_2、R_4及R_8各自為H；

R_3為C_1-C_4烷基；及

R_5為NH_2，視情況其中自裂解二肽之第一個胺基酸呈D-構形。

[0118] 在一個實施例中，本文揭示之GLP-1拮抗劑肽及二聚體與以下結構之自裂解二肽共價連接：



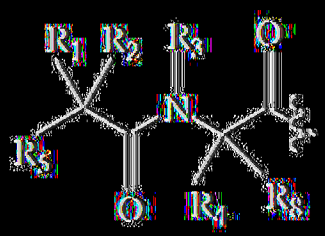
其中

R_1為選自由以下組成之群的側鏈：C_1-C_{18}烷基、(C_1-C_4烷基)OH、(C_1-C_4烷基)SH、(C_1-C_4烷基)COOH及(C_1-C_4烷基)NH_2，視情況其中C16-C20脂肪酸或C16-C20二酸與該側鏈共價連接；

R_2、R_4及R_8獨立地為H或C_1-C_4烷基；

R_3為C_1-C_4烷基，或R_4及R_3與其所連接之原子一起形成吡咯啶環；且R_5為NH_2，其限制條件為當R_4及R_3與其所連接之原子一起形成吡咯啶環時，R_2不為H。

[0119] 在另一實施例中，自裂解二肽具有以下之結構：



其中R_1為(C1-C4烷基)NH-CO(CH_2)14-20CH_3、(C1-C4烷基)NH-[間隔子]-CO(CH_2)14-20CH_3、(C1-C4烷基)NH-CO(CH_2)14-20COOH或(C1-C4烷基)NH-[間隔子]-CO(CH_2)14-20COOH；R_2及R_8各自為H；R_4為H或CH_3；R_3為C1-C4烷基且R_5為NH_2，視情況其中自裂解二肽之第一個胺基酸為呈D-立體化學組態之胺基酸，且間隔子選自本文揭示之間隔子中之任一者。在一個實施例中，R_2、R_4及R_8各自為H。在一個實施例中，R_1為(C1-C4烷基)NH-CO(CH_2)16COOH或(C1-C4烷基)NH-[間隔子]-CO(CH_2)16COOH，R_2、R_4及R_8各自為H且R_3為C1-C4烷基，視情況為CH_3，視情況其中間隔子包含以下結構：

-[$COCH_2(OCH_2CH_2)_kNH]_q$-(γ麩胺酸)$_p$-

其中k為2，且p及q獨立地為選自1或2之整數。

[0120] 根據一個實施例，自裂解二肽包含醯化胺基酸作為第一個胺基酸，其中醯化胺基酸之側鏈經C16-C20脂肪酸或C16-C20二酸醯化，視情況其中醯化胺基酸選自C16-C20醯化離胺酸、C16-C20醯化鳥胺酸、C16-C20醯化半胱胺酸及C16-C20醯化高半胱胺酸，視情況其中二肽之醯化胺基酸為C16-C20醯化Lys，視情況其中自裂解二肽之第一個胺基酸為呈D-立體化學組態之胺基酸。

[0121]

實施例

根據實施例1，提供一種GLP-1受體拮抗劑，其中該拮抗劑包含胺基酸序列 R_{10}-DV$X_{11}X_{12}$YL$X_{15}X_{16}$QA$X_{19}X_{20}$EFX_{23}EWLVRGGPSSGAPPPSX_{40}-R_{20}

(SEQ ID NO: 23)，其中

R_{10}為NH_2或1或2個胺基酸之N端延伸部分，其中N端延伸部分之一個胺基酸經C14-C20脂肪酸或二酸醯化(視情況經由間隔子)，視情況其中R_{10}為結構：X_7X_8之二肽，其中X_7為醯化胺基酸，視情況為醯化Lys或醯化dLys，且X_8為Gly或C_1-C_4 N-烷基化Gly；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg或醯化胺基酸，視情況為醯化Lys；

X_{15}為Glu或dGlu；

X_{16}為Glu、dGlu、Asp、高麩胺酸或高氧化半胱胺酸；

X_{19}為Val、環丙烷、環戊烷、環己烷或苯基甘胺酸；

X_{20}為Arg、高離胺酸或瓜胺酸；

X_{23}為Ile或dIle；及

X_{40}為醯化胺基酸，視情況為醯化Lys；及

R_{20}為COOH或$CONH_2$，視情況其中1、2或3個選自位置7、10、13或16之胺基酸經Trp或dTrp取代，其限制條件為當X_{10}或X_{11}中之一者為Trp或dTrp時，則另一者不為Trp或dTrp，及R_{10}及X_{12}不能均包含醯化胺基酸；視情況其中1、2或3個在位置16、18、19、24、26或28中之任一者處之胺基酸經Aib取代。

【0122】根據實施例2，提供如實施例1之GLP-1拮抗劑，其中該拮抗劑包含胺基酸序列R_{10}-$DVX_{11}X_{12}YLX_{15}X_{16}QAX_{19}X_{20}EFX_{23}EWLVRGGPSSGAPPPSX_{40}$-$R_{20}$ (SEQ ID NO: 23)，其中

R_{10}為NH_2或X_7X_8，其中X_7為經C14-C20脂肪酸或二酸醯化之胺基酸

(視情況經由間隔子)，且X_8為Gly或C_1-C_4 N-烷基化Gly；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg或醯化胺基酸，視情況為醯化Lys；

X_{15}為Glu或dGlu；

X_{16}為Glu、dGlu、Asp、高麩胺酸或高氧化半胱胺酸；

X_{19}為Val、環丙烷、環戊烷、環己烷或苯基甘胺酸；

X_{20}為Arg、高離胺酸或瓜胺酸；

X_{23}為Ile或dIle；及

X_{40}為醯化胺基酸，視情況為醯化Lys；及

R_{20}為COOH或$CONH_2$，視情況其中1、2或3個在位置16、18、19、24、26或28中之任一者處之胺基酸經Aib取代。

【0123】 根據實施例3，提供如實施例1或2之GLP-1拮抗劑，其中該GLP-1拮抗劑之各醯化胺基酸為醯化Lys。

【0124】 根據實施例4，提供如實施例1至3中任一項之GLP-1拮抗劑，其中X_7為醯化Lys且X_{12}為Arg。

【0125】 根據實施例5，提供如實施例1至3中任一項之GLP-1拮抗劑，其中R_{10}為NH_2且X_{12}為醯化Lys。

【0126】 根據實施例6，提供如實施例1至3中任一項之GLP-1拮抗劑，其中X_7為NH_2且X_{12}為Arg。

【0127】 根據實施例7，提供如實施例1之GLP-1拮抗劑，該拮抗劑包含選自SEQ ID NO: 5至SEQ ID NO: 96中之任一者或其任何組合的胺基酸序列。

【0128】 根據實施例8，提供如實施例1至7中任一項之GLP-1拮抗

劑，其中該GLP-1拮抗劑之醯化胺基酸獨立地為經直接與Lys側鏈連接或視情況經由包含以下之間隔子連接之C16-C18脂肪酸或C16-C18脂肪二酸醯化的Lys殘基：

(i) γ麩胺酸，

(ii) minipeg聚合物：-[$COCH_2(OCH_2CH_2)_kNH$]-，其中k為2、4、6或8，

(iii)或i)及/或ii)之任何倍數(multiplicity)或組合。

【0129】 根據實施例9，提供如實施例1至8中任一項之GLP-1拮抗劑，其中該拮抗劑包含以下之胺基酸序列：

$DX_{10}X_{11}RYLX_{15}X_{16}QAVREFX_{23}EWLVRGGPSSGAPPPSX_{40}R_{20}$ (SEQ ID NO: 5)，其中

X_{10}為Trp、dTrp或Val；

X_{11}為Trp、dTrp或Ser；

X_{15}為Glu或dGlu

X_{16}為Trp、dTrp、dGlu或Glu；

X_{23}為Ile或dIle；

X_{40}為醯化胺基酸；及

R_{20}為COOH或$CONH_2$，視情況其中肽在位置16、18、19、24、26或28中之任一者處包含一或多個Aib取代，或視情況在位置12處包含醯化Lys取代，其中該位置編號係相對於原生艾塞那肽4胺基酸序列。

【0130】 根據實施例10，提供如實施例1至9中任一項之GLP-1拮抗劑，其中X_{11}為Trp或dTrp。

【0131】 根據實施例11，提供如實施例1至10中任一項之GLP-1拮

抗劑，其中在SEQ ID NO: 5之位置16、18、19、24、26或28中之任一者處之胺基酸經Aib取代，視情況其中Aib係在位置18處取代。

【0132】 根據實施例12，提供如實施例1至11中任一項之GLP-1拮抗劑，其中位置12處之胺基酸經醯化Lys取代。

【0133】 根據實施例13，提供如實施例1至11中任一項之GLP-1拮抗劑，其中

X_{15}為dGlu；

X_{16}為Glu；及

X_{23}為Ile。

【0134】 根據實施例14，提供如實施例1至11中任一項之GLP-1拮抗劑，其中

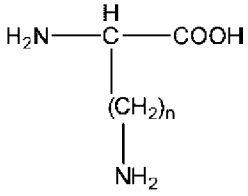
X_{15}為Glu；

X_{16}為Glu；及

X_{23}為Ile。

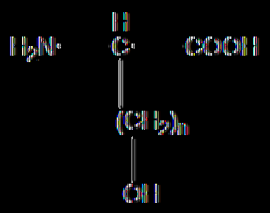
【0135】 根據實施例15，提供如實施例1至14中任一項之GLP-1拮抗劑，其中X_{40}為醯基視情況經由間隔子與胺基酸之側鏈連接之胺基酸。

【0136】 根據實施例16，提供如實施例1至15中任一項之GLP-1拮抗劑，其中X_{40}為包含式I (視情況，Lys)、式II (視情況，Cys)或式III (視情況，Ser)之結構的胺基酸，其中式I、II及III中之各者為：



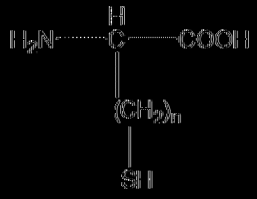
其中n = 1至4

[式I]；



其中n = 1至4

[式II]；及



其中n = 1至4

[式III]。

[0137] 根據實施例17，提供如實施例1至16中任一項之GLP-1拮抗劑，其中X_{10}為醯化離胺酸。

[0138] 根據實施例18，提供如實施例1至17中任一項之GLP-1拮抗劑，其中醯化胺基酸之醯基選自(C1-C4烷基)NH-CO$(CH_2)_{14-20}CH_3$、(C1-C4烷基)NH-[間隔子]-CO$(CH_2)_{14-20}CH_3$、(C1-C4烷基)NH-CO$(CH_2)_{14-20}$COOH或(C1-C4烷基)NH-[間隔子]-CO$(CH_2)_{14-20}$COOH。

[0139] 根據實施例19，提供如實施例1至18中任一項之GLP-1拮抗劑，其中醯化胺基酸之醯基經由間隔子與醯化胺基酸之胺基酸側鏈共價連接。

[0140] 根據實施例20，提供如實施例1至19中任一項之GLP-1拮抗劑，其中間隔子為胺基酸或二肽。

[0141] 根據實施例21，提供如實施例1至20中任一項之GLP-1拮抗劑，其中間隔子包含

(i) γ麩胺酸，

(ii) minipeg聚合物：-[$COCH_2(OCH_2CH_2)_kNH$]-，其中k為2、4、6或8，

(iii)或i)及/或ii)之任何倍數或組合。

【0142】 根據實施例22，提供如實施例1至11中任一項之GLP-1拮抗劑，其中醯化胺基酸與C16至C18脂肪酸或C16至C18脂肪二酸連接，視情況其中酸或二酸係經由包含以下結構之間隔子連接：

-(γ麩胺酸)$_p$-[$COCH_2(OCH_2CH_2)_kNH$]$_q$-(γ麩胺酸)$_n$-

或

-[$COCH_2(OCH_2CH_2)_kNH$]$_q$-(γ麩胺酸)$_p$-[$COCH_2(OCH_2CH_2)_kNH$]$_m$-；

其中k為選自2、4或8之整數，m及n獨立地為選自0、1或2之整數，且p及q獨立地為選自1、2、4或8之整數。

【0143】 根據實施例23，提供如實施例1至22中任一項之GLP-1拮抗劑，其中醯化胺基酸為C16至C18脂肪酸經由包含以下結構之間隔子與離胺酸側鏈連接的Lys：

-[$COCH_2(OCH_2CH_2)_kNH$]$_q$-(γ麩胺酸)$_p$-

其中k為2，且p及q獨立地為選自1或2之整數。

【0144】 根據實施例24，提供如實施例1至23中任一項之GLP-1拮抗劑，其中

X_{11}為Trp或dTrp；

X_{15}為Glu或dGlu；

X_{16}為Glu或dGlu；

X_{23}為Ile或dIle；及

X_{40}為經C16或C18二酸醯化之Lys，視情況其中二酸係經由包含以下

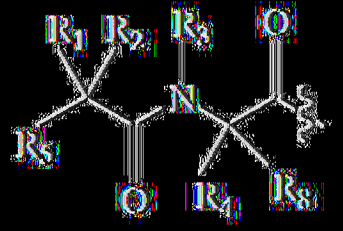
結構之間隔子連接：

$-[COCH_2(OCH_2CH_2)_kNH]_q-(\gamma$麩胺酸$)_p-$

其中k為2，且p及q獨立地為選自1或2之整數。

[0145] 根據實施例25，提供如實施例1至24中任一項之GLP-1拮抗劑，其中R_{20}為$CONH_2$。

[0146] 根據實施例26，提供如實施例9至25中任一項之GLP-1拮抗劑之衍生物，其進一步包含二肽A-B：



其經由醯胺鍵與該GLP-1拮抗劑連接，其中

R_1、R_2、R_4及R_8獨立地選自由以下組成之群：H、C_1-C_{18}烷基、C_2-C_{18}烯基、(C_1-C_{18}烷基)OH、(C_1-C_{18}烷基)SH、(C_2-C_3烷基)SCH_3、(C_1-C_4烷基)$CONH_2$、(C_1-C_4烷基)COOH、(C_1-C_4烷基)NH_2、(C_1-C_4烷基)$NHC(NH_2^+)NH_2$、(C_0-C_4烷基)(C_3-C_6環烷基)、(C_0-C_4烷基)(C_2-C_5雜環)、(C_0-C_4烷基)(C_6-C_{10}芳基)R_7、(C_1-C_4烷基)(C_3-C_9雜芳基)及C_1-C_{12}烷基(W1)C_1-C_{12}烷基，其中W1為選自由N、S及O組成之群的雜原子；

R_3選自由以下組成之群：C_1-C_{18}烷基、(C_1-C_{18}烷基)OH、(C_1-C_{18}烷基)NH_2、(C_1-C_{18}烷基)SH、(C_0-C_4烷基)(C_3-C_6)環烷基、(C_0-C_4烷基)(C_2-C_5雜環)、(C_0-C_4烷基)(C_6-C_{10}芳基)R_7及(C_1-C_4烷基)(C_3-C_9雜芳基)，或R_4及R_3與其所連接之原子一起形成吡咯啶環；

R_5為NHR_6或OH；

R_6為H、C_1-C_8烷基；及

R_7選自由H及OH組成之群，

其中在生理條件下在PBS中，A-B自該GLP-1拮抗劑之化學裂解半衰期($t_{1/2}$)為至少約1小時至約1週。

【0147】 根據實施例27，提供如實施例26之GLP-1拮抗劑，其中二肽A-B與GLP-1拮抗劑胺基酸序列之N端α胺共價連接。

【0148】 根據實施例28，提供如實施例26至27中任一項之GLP-1拮抗劑，其中

R_1及R_8獨立地為H或C_1-C_8烷基；

R_2及R_4獨立地選自由以下組成之群：H、C_1-C_8烷基、(C_1-C_4烷基)OH、(C_1-C_4烷基)SH、(C_2-C_3烷基)SCH_3、(C_1-C_4烷基)$CONH_2$、(C_1-C_4烷基)COOH、(C_1-C_4烷基)NH_2及(C_1-C_4烷基)(C_6芳基)R_7；

R_3為C_1-C_6烷基；

R_5為NH_2；及

R_7選自由氫及OH組成之群。

【0149】 根據實施例29，提供如實施例26至27中任一項之GLP-1拮抗劑，其中

R_1包含選自由組成之群的側鏈：C_1-C_8烷基、(C_1-C_4烷基)OH、(C_1-C_4烷基)SH、(C_1-C_4烷基)COOH及(C_1-C_4烷基)NH_2，視情況其中C16-C30脂肪酸或C16-C30二酸視情況經由選自由組成之群之間隔子與該側鏈共價連接：γ麩胺酸、γ麩胺酸-γ麩胺酸二肽及γ麩胺酸-$[COCH_2(OCH_2CH_2)_kNH]_q$-γ麩胺酸，其中

k為選自1-8之範圍之整數；及

q為選自1-8之範圍之整數，視情況其中k為2且q選自1-8之範圍；

R_2、R_4及R_8獨立地為H或C_1-C_4烷基；

R_3為C_1-C_6烷基；及

R_5為NH_2。

【0150】 根據實施例30，提供如實施例26至29中任一項之GLP-1拮抗劑，其中

R_1為H、C_1-C_4烷基、(C_1-C_4烷基)OH或(C_1-C_4烷基)NH_2；

R_2為H，

R_3為C_1-C_4烷基；

R_4為H或C_1-C_4烷基；

R_5為NH_2；及

R_8為氫。

【0151】 根據實施例31，提供如實施例26至30中任一項之GLP-1拮抗劑，其中該二肽A-B包含醯化Lys殘基及N-烷基化Gly殘基，其中該Lys殘基及該N-烷基化Gly殘基係經由肽鍵連接，視情況其中該Lys殘基係呈D-構形。

【0152】 根據實施例32，提供如實施例26至30中任一項之GLP-1拮抗劑，其中

R_1為(C_4烷基)NH_2或(C_4烷基)NH(mPeg-γE-二酸)-C18；

R_2、R_4及R_8各自為H；

R_3為C_1-C_4烷基；且R_5為NH_2；

R_5為胺。

【0153】 根據實施例33，提供一種醫藥組合物，其包含如實施例1至32中任一項之GLP-1拮抗劑或衍生物，及醫藥學上可接受之載劑、稀釋劑或賦形劑。

【0154】 根據實施例34提供一種治療罹患非典型低血糖症之患者之方法，其中該方法包含以有效提高血糖水平之量向有需要之患者投與如實施例33之醫藥組合物的步驟。

【0155】

實例1

Ex-4 (9-39)a (SEQ ID NO: 2)為確立的GLP-1受體拮抗劑。然而，其用作人類中之治療劑受到限制，此係由於其非人類來源且其相對較短的活體內作用持續時間。人類GLP-1之相當的N端縮短減輕促效作用但不會提供高效能拮抗劑。經由一系列GLP-1/Ex-4雜交肽，產生純的基於GLP-1之拮抗劑所需的極小結構變化鑑別為Glu16、Val19及Arg20，產生相較於Ex-4 (9-39)a活體外效能大約高3倍的拮抗劑。基於人類之拮抗劑之位點特異性醯化產生效能增加且相對於GIP受體具有10倍更高選擇性之肽「9-40 Jant4 K_{40}[C16] (SEQ ID NO: 3)」作為GLP-1受體拮抗劑(Patterson等人, ACS Chem. Biol. 2011, 6, 135-145)。

【0156】 如本文所揭示，已製備9-40 Jant4-K_{40}之變體以提供進一步改良的GLP-1受體拮抗劑。肽9-40 Jant4-K_{40}在位置40處藉由將C16醯基與Lys側鏈直接鍵聯而醯化。已製備插入間隔子於Lys側鏈與C16醯基之間的變體。表2呈現此等醯化變體之GLP-1拮抗劑活性及溶解性。

【0157】 對 9-40Jant4-K_{40} (DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSK；SEQ ID NO: 3)之一級序列進行各種胺基酸取代，且此等變體之GLP-1拮抗劑活性及溶解性提供於表3中。

【0158】 表4提供關於Aib取代對Jant4-K_{40} (SEQ ID NO: 3)變體之活性及溶解性之影響的資料。表5提供關於d-AA取代對Jant4-K_{40} (C16)

(SEQ ID NO: 3)變體之溶解性之影響的資料，且表6呈現關於在Jant4-K_{40} (SEQ ID NO: 3)之位置3處之Trp取代的資料。

【0159】

材料及方法

【0160】

Fmoc合成

藉由自動Fmoc/t-Bu固相方法，採用Symphony肽合成器((Peptide Tech-nology, Tucson, AZ)，以Wang樹脂(AAPPtec, Louisville, KY)起始及6-Cl-HOBt/DIC活化製備肽。所有習知殘基均係購自Midwest Biotech (Fisher, IN)，6-Cl- HOBt及DIC係獲自AAPPtec (Louisville, KY)。肽自樹脂裂解且藉由用含有2.5% TIS、2.5% H_2O、1.5%甲醇、2.5%苯酚、0.5% DODT及0.5%二甲亞碸之TFA處理脫除保護基。根據標準程序，用冷乙醚自過濾的TFA溶液沈澱出肽。在樹脂上用十倍過量之Fmoc-Glu-OtBu/DEPBT/DIEA (重複以進行二次偶聯)，隨後用十倍過量之棕櫚酸或另一脂肪酸/DEPBT/DIEA進行肽之脂肪-醯化。

【0161】

拮抗劑醯化

使用正交固相保護流程，將棕櫚酸引入合成的拮抗劑肽。使用Boc合成來進行肽合成，從而允許在Lys40選擇性引入鹼敏感性側鏈保護的Lys(Fmoc)-OH。完全保護的肽在樹脂上用含20%吡啶之DMF (v/v)處理30 min以移除Lys40側鏈Fmoc基團。

【0162】 用過量脂肪酸及5當量含苯并三唑-1-基-氧基三吡咯啶基鏻六氟磷酸鹽(PyBOP) (Fluka)之DCM/DIEA (4:1 v/v)促進醯胺鍵形成持續

大約18 h。使用茚三酮測試來監測反應進展，且在肽裂解之後藉由ESI質譜確認醯化。

【0163】

肽純化

使用逆相HPLC (RP-HPLC)來進行肽純化。在製備型RP-HPLC純化期間，用線性乙腈/0.1%三氟乙酸梯度使用C18固定相(Vydac 218TP, 250 mm _ 22 mm, 10 μm)。藉由採用利用C8管柱(Zorbax 300SB, 4.6 mm X 50 mm, 3.5 μm)RP-HPLC對於峰溶離份進行分析性分析。藉由分析性RP-HPLC及ESI-或MALDI-質譜評定肽一致性及純度。發現所有肽均具有正確分子量且大約為95%純。將凍乾肽儲存在4℃。

【0164】

GLP-1受體介導之cAMP誘導

【0165】 藉由基於螢光素酶之報導基因分析檢查肽刺激或阻斷在GLP-1受體之cAMP誘導的能力。用人類GLP-1受體(Open Biosystems)及cAMP誘導性(cAMP反應元件)螢光素酶基因共轉染HEK 293細胞構成其中可量測受體活化之細胞構築體。生物分析藉由如下來進行：首先在補充0.25%牛生長血清(HyClone)之杜爾貝寇改良伊格爾培養基(Dulbecco's modified Eagle's medium) (Invitrogen)中血清剝奪細胞16 h，且接著添加在適當濃度範圍內之肽的連續稀釋液於96孔聚D-離胺酸塗覆盤(BD Biosciences)中。對於拮抗作用分析而言，在稀釋的肽之後，添加恆定濃度之GLP-1 (0.05 nM)至分析盤。在37℃、5% CO_2下繼續培育5 h，且隨後添加當量體積(100 μL)之LucLite發光受質試劑(Perkin-Elmer)。MicroBeta 1450液體閃爍計數(Perkin-Elmer)定量在600 rpm下振盪培養盤

3 min後呈每秒計數(cps)之發光訊號。使用Origin軟體(OriginLab)繪製資料，且藉由S形擬合測定有效濃度50 (EC_{50})或抑制濃度50 (IC_{50})。藉由相對EC_{50}或IC_{50}值之比較性分析測定效能。各實驗重複至少三次，其中分析各樣本重複兩次。

動物

C57Bl/6小鼠係獲自傑克遜實驗室(Jackson Laboratories)。以在22℃下，自由獲取食物及水之12:12 h光-暗循環單隻或群組圈養小鼠。所有研究已經批准且根據辛辛那提大學機構動物照護及使用委員會(Institutional Animal Care and Use Committee of the University of Cincinnati)之指南進行。

【0166】

葡萄糖耐受性測試(GTT)

對於葡萄糖耐受性之測定而言，使小鼠經歷6 h禁食且腹膜內注射葡萄糖。注射由1.5 g葡萄糖/kg體重(含25% w/v D-葡萄糖(Sigma)之0.9% w/v鹽水)組成。在注射前0 min及在注射後15、30、60及120 min，使用手持式血糖儀(FreeStyle Freedom Lite)量測尾部血糖水平($mg \cdot dL^{-1}$)。

【0167】

急性活體內研究

在用IP注射二肽基肽酶-IV保護的Ex-4 (0.65 nmol·kg-1)刺激之前，小鼠在1、4、8、24、48、72或120接受皮下注射變化劑量之肽(於PBS中)。在GLP-1注射後十五分鐘進行GTT。如上文所描述獲得尾部血糖值。

表2：對於Jant 4-K_{40}序列(SEQ ID NO: 3)之C16連接子最佳化/分析

編號	**9-40醯胺; Jant 4 K40[X]**	生物活性 **IC_{50}**	SDV	N	**溶解性 [mg/mL] 80 mM AmBicarb pH 7.7**
95	游離胺	**281**	96	3	12.7
47	C16	**14**	7	15	6.1
52	γE-16	**12**	3	7	>20
53	γE_2-C16	**13**	5	10	>20
54	γE_4-C16	**21**	8	8	>20
55	γE_6-C16	**22**	15	5	>20
48	$(miniPEG)_2\gamma E$-C16	**9**	4	7	9.0
56	MiniPEG-γE-C16	**14**	2	3	>20
57	gE-$Mini(PEG)_2$-gE-C16	**9**	7	5	>25
58	$(mini)PEG_2$-gE_2-16				>25
59	miniPEG-gE-miniPEG-gE-C16	**11**	7	5	>25
60	miniPEG-gE_2 miniPEG-C16	**5**	2	5	>25
61	gE_2-$(miniPEG)_2$-C16	**6**	2	4	>25
62	gE-miniPEG-gE-C16 miniPEG-	**7**	3	4	>25
63	二酸C18	**114**	54	16	>25
64	gE_2-二酸C18	**841**	361	7	>25
65	gE_4-二酸C18	**1071**	624	8	>25
66	gE_6-二酸C18	**1464**	751	6	>25
67	$(miniPEG)_2$-gE-二酸C18	**579**	376	12	>25
68	miniPEG-gE二酸C18	**718**	130	3	>25

表3：Jant4-K_{40} (SEQ ID NO: 3)之胺基酸取代變體

編號	9-40;Jant4	K40[C16]	生物活性 **IC_{50}**	SDV	N	**溶解性** 80 mM AmeBicarb pH 7.7
47		-醯胺	**14**	7	15	**6.1**
69	R28	-醯胺	**16**	1	3	**13.7‡**
70	E24, R28	-醯胺	**14**	4	4	**>20**
71	E17, R28	-醯胺	**18**	7	4	**>20**
72	E17,E24,R28	-醯胺	**19**	6	4	**>20**
73	R12, R28	-醯胺	**27**	17	4	**<0.1**
74	R12, E24,R28	-醯胺	**15**	3	4	**>20**

75	R12,E17,E24,R28	-醯胺	**19**	5	4	**18.6**
76	艾塞那肽K40	-醯胺	**6**	1	3	**18.6**
77		R28¥ -酸	**13**	2	5	**>20**
78	E24,	R28¥ -酸	**19**	13	13	**>20**
16	R12, E24,	R28¥ -酸	**18**	12	13	**>20**
79	E24, R27	v28¥ -酸	**115**	37	10	**>20**
80	E24, R27	Aib28¥ -酸	**106**	1414		**>20**

¥ K40[miniPEG-gE-C16]

‡高黏稠溶液

表4：Aib對Jant4-K_{40} (SEQ ID NO: 3)之活性及溶解性之影響

編號	**9-40am; Jant4 k40[C16]**	生物活性			溶解性 [mg/mL] 80 mM AmBicarb pH7.7	溶解性 [mg/mL] PBS pH 7.7
		IC_{50}	SDV	N		
81	Aib27	**23**	10	4	19.0 (6.1)	1.6
4328	K27, Aib28	**13**	13	10	18.9 (5.10	0.2
82	K26, Aib	**6**	2	4	14.2 (6.0)	0.1
44	Aib26	**8**	1	4	19.0 (5.7)	0.1
83	Aib24	**14**	6	4	12.6 (4.2)	0.3
45	Aib19	**8**	2	4	11.1 (1.6)	0.4
46	Aib18	**7**	2	3	17.5 (3.5)	0.7
84	Aib16	**30**	13	3	5.2 (0.2)	0.2

表5：用d-AA改良Jant4-K_{40} (C16) (SEQ ID NO: 3)之溶解性

編號	**9-40am; Jan54 K40[C16]**	**生物活性**			溶解性[mg/mL] 80 mM/AmBicarb pH 7.7
		KC_{50}	SDV	**N**	
49	*d-Glu_{25}*	**23**	12	**7**	**>20**
85	*d-Glu_{16}*	**41**	20	**7**	**10.7**
86	*d-Gln_{17}*	**41**	24	**6**	**2.2**
50	*d-Val_{19}*	**124**	86	**6**	**>20**
87	*d-Arg_{20}*	**16**	6	**4**	**0.8**
88	*d-Glu_{21}*	**27**	13	**4**	**1.7**
51	*d-HE_{23}*	**31**	12	**5**	**>20**

表6：在Jant4-K40 (SEQ ID NO: 3)之位置3處之Trp取代

SEQ ID NO: #	**結構**	**IC50 (nM)**
89	Ex9-39醯胺, dK7(PEG2-γE(C16)), G8	6.2
90	Ex9-40醯胺, K40(C18二酸)	28
91	Ex9-40醯胺, W11, K40(C18二酸)	43
92	Ex9-40醯胺, dW11, K40(C18二酸)	32
93	Ex9-40醯胺, W11, K40(mPeg-γE-C18二酸)	87
94	Ex9-40醯胺, dW11,K40(mPeg-γE-C18二酸)	115

【0168】

實例2

【0169】

MBX-1416之合成程序：

用在0.1 mmol標度之Fmoc-Ser(tBu)-Wang之起始固相樹脂進行MBX-1416之合成。一旦自Fmoc-Ser(tBu)-Wang樹脂移除第一個Fmoc-基團，則依序將構成殘基9至38 (Asp9-Pro38)之Fmoc-胺基酸與游離N端胺偶聯。使用如下表中所示之標準Fmoc/DIC/Oxyma合成方案，採用ABI肽合成儀用於自動組裝。

ABI433A合成儀上使用之Fmoc_DIC_Oxyma_0.10 mmol方案之細節

偶聯試劑		Fmoc保護的胺基酸	溶劑	活化時間	偶聯時間	脫除保護基
含1M DIC之NMP (1.0 mL)	含1M Oxyma之NMP (1.0 mL)	1.0 mmol筒	NMP及DCM	16 min	37 min	含20%哌啶之DMF，11 min

【0170】

C18二酸偶聯程序：

一旦已組裝完全Asp9至Ser39肽，則將N端C18二酸偶聯至肽基樹脂。使用含DIC (1 mmol)及Oxyma (1 mmol)之DMF，將其引入作為三級丁基保護的C18二酸(1 mmol)。將三級丁基的保護C18二酸(1 mmol)及Oxyma (1 mmol)溶解於DMF (10 mL)中。向此混合物中添加DIC (1 mmol)且使其在室溫下預活化10-15 min。將此反應混合物添加至Asp9-Ser39肽基樹脂且在室溫下在攪動下進行偶聯4 h。

【0171】

MBX-1416純化：

藉由Waters HPLC控制器600，使用Gemini® 10μm C8 100 Å, LC 250X21.2 mm逆相管柱(目錄號00G-4763-PO- AX)，與自80% A + 20% B至20% A + 80% B之線性梯度90 min，15 ml/min之流速來純化MBX-1416。兩種緩衝液由0.1% TFA/10%乙腈+ 90% H_2O (緩衝液A)及0.1% TFA/100%乙腈(緩衝液B)組成。

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【發明申請專利範圍】

【請求項1】

一種GLP-1受體拮抗劑，該拮抗劑包含以下之胺基酸序列：

R_{10}-DV$X_{11}X_{12}$YL$X_{15}X_{16}$QA$X_{19}X_{20}$EF$X_{23}X_{24}$WLVRGGPSSGAPPPS-R_{20} SEQ ID NO: 97)，其中

R_{10}為與該GLP-1拮抗劑胺基酸序列之N端α胺共價連接之C14-C20脂肪酸或二酸；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg或Ser；

X_{15}為Glu或dGlu；

X_{16}為Glu、dGlu、Asp、高麩胺酸或高氧化半胱胺酸；

X_{19}為Val、環丙烷、環戊烷、環己烷或苯基甘胺酸；

X_{20}為Arg、高離胺酸或瓜胺酸；

X_{23}為Ile或dIle；

X_{24}為Glu或Ala；及

R_{20}為COOH或$CONH_2$，視情況其中基於原生艾塞那肽4 (Exendin4) (SEQ ID NO: 1)之編號，位置16、18、19、24、26或28中之任一者處之1、2或3個胺基酸經Aib取代。

【請求項2】

如請求項1之GLP-1拮抗劑，其中該拮抗劑包含以下之胺基酸序列：

R_{10}-DV$X_{11}X_{12}$YL$X_{15}X_{16}$QA$X_{19}X_{20}$EFX_{23}EWLVRGGPSSGAPPPS-R_{20} SEQ ID NO: 99)，其中

R_{10}為與該GLP-1拮抗劑胺基酸序列之N端α胺共價連接之C14-C20

脂肪酸或二酸；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg或Ser；

X_{15}為Glu或dGlu；

X_{16}為Glu、dGlu、Asp、高麩胺酸或高氧化半胱胺酸；

X_{19}為Val；

X_{20}為Arg、高離胺酸或瓜胺酸；

X_{23}為Ile或dIle；及

R_{20}為COOH或$CONH_2$，視情況其中基於原生艾塞那肽4 (SEQ ID NO: 1)之編號，位置16、18、19、24、26或28中之任一者處之1、2或3個胺基酸經Aib取代。

【請求項3】

如請求項1或2之GLP-1拮抗劑，其中

R_{10}為$-CO(CH_2)_{14-20}CH_3$或$-CO(CH_2)_{14-20}COOH$；

X_{11}為Trp、dTrp或Ser；

X_{12}為Ser；

X_{15}為Glu或dGlu；

X_{16}為Glu或dGlu；

X_{19}為Val；

X_{20}為Arg；

X_{23}為Ile或dIle；及

R_{20}為COOH。

【請求項4】

如請求項1至3中任一項之GLP-1拮抗劑，其中R_{10}為與該GLP-1拮抗劑胺基酸序列之N端α胺共價連接之-$CO(CH_2)_{16-18}COOH$。

【請求項5】

如請求項1至4中任一項之GLP-1拮抗劑類似物，其中基於原生艾塞那肽4 (SEQ ID NO: 1)之編號，位置16、18、19、24、26或28處之胺基酸經Aib取代。

【請求項6】

如請求項1至6中任一項之GLP-1拮抗劑類似物，其進一步包含1-3個胺基酸之C端延伸部分，視情況其中該C端延伸部分之胺基酸中之一者包含醯化胺基酸，視情況醯化Lys。

【請求項7】

一種GLP-1受體拮抗劑，該拮抗劑包含以下之胺基酸序列：

R_{10}-D$X_{10}X_{11}X_{12}$YL$X_{15}X_{16}$QAVREF$X_{23}X_{24}$WLVRGGPSSGAPPPS-R_{20} (SEQ ID NO: 98)；其中

R_{10}為與該GLP-1拮抗劑胺基酸序列之N端α胺共價連接之C14-C20脂肪酸或二酸；

X_{10}為Trp、dTrp或Val；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg、Lys或Ser；

X_{15}為Glu或dGlu；

X_{16}為Trp、dTrp、dGlu或Glu；

X_{23}為Ile或dIle；

X_{24}為Ala或Glu；及

R_{20}為COOH或$CONH_2$。

【請求項8】

如請求項7之GLP-1受體拮抗劑，其中

R_{10}為與該GLP-1受體拮抗劑之N端α胺連接之-$CO(CH_2)_{14-20}CH_3$或-$CO(CH_2)_{14-20}COOH$；

X_{10}為Trp、dTrp或Val；

X_{11}為Trp、dTrp或Ser；

X_{12}為Arg、Lys或Ser；

X_{15}為Glu或dGlu；

X_{16}為Trp、dTrp、dGlu或Glu；

X_{23}為Ile或dIle；及

X_{24}為Ala或Glu。

【請求項9】

一種GLP-1受體拮抗劑，該拮抗劑包含R_{10}-DVSSYLEEQAVREFIAWLVKGGPSSGAPPPS-R_{20} (SEQ ID NO: 3)之胺基酸序列或與SEQ ID NO: 3相差1、2或3個胺基酸取代同時保留GLP-1促效劑活性之胺基酸序列，其中

R_{10}為與該GLP-1受體拮抗劑之N端α胺連接之-$CO(CH_2)_{14-20}CH_3$或-$CO(CH_2)_{14-20}COOH$；及

R_{20}為COOH或$CONH_2$。

【請求項10】

如請求項9之GLP-1受體拮抗劑，其中該GLP-1受體拮抗劑在位置16、18、19、24、26或28之任何組合處包含一至三個Aib取代，其中該位

置編號係相對於原生艾塞那肽4胺基酸序列。

【請求項11】

如請求項9或10之GLP-1受體拮抗劑，其中

R_{10}為$-CO(CH_2)_{14-20}COOH$；及

R_{20}為COOH。

【請求項12】

如請求項7至11中任一項之GLP-1拮抗劑，其中X_{11}為Trp或dTrp。

【請求項13】

如請求項7至12中任一項之GLP-1拮抗劑，其中位置16、18、19、24、26或28處之胺基酸經Aib取代。

【請求項14】

如請求項9至13中任一項之GLP-1拮抗劑，其中

X_{15}為dGlu；

X_{16}為Glu；及

X_{23}為Ile。

【請求項15】

如請求項9至13中任一項之GLP-1拮抗劑，其中

X_{15}為Glu；

X_{16}為Glu；及

X_{23}為Ile。

【請求項16】

如請求項9至15中任一項之GLP-1拮抗劑，其進一步包含醯基視情況經由間隔子與胺基酸之側鏈連接之該胺基酸的C端延伸部分。

【請求項17】

如請求項16之GLP-1拮抗劑，其中該醯化胺基酸為醯化離胺酸。

【請求項18】

如請求項16或17之GLP-1拮抗劑，其中該醯化胺基酸之醯基經由間隔子與該醯化胺基酸之胺基酸側鏈共價連接，視情況其中該間隔子包含

i) γ麩胺酸，

ii) minipeg聚合物：-[$COCH_2(OCH_2CH_2)_kNH$]-，其中k為2、4、6或8，

iii)或i)及/或ii)之任何倍數(multiplicity)或組合。

【請求項19】

如請求項9至18中任一項之GLP-1拮抗劑，其中R_{20}為$CONH_2$。

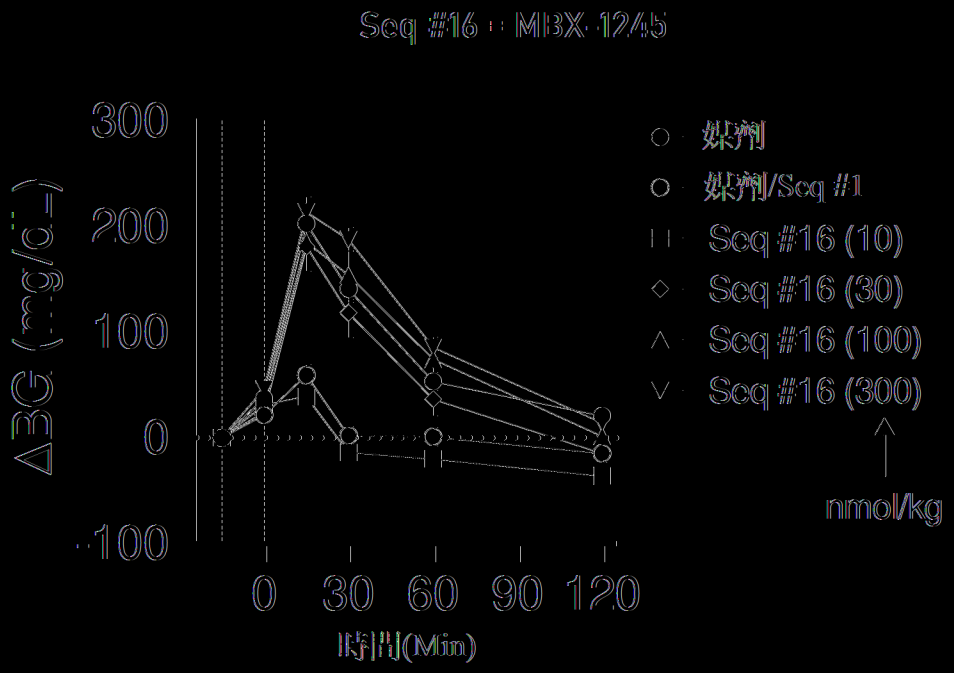
【請求項20】

一種醫藥組合物，其包含如請求項1至19中任一項之GLP-1拮抗劑及醫藥學上可接受之載劑、稀釋劑或賦形劑。

【請求項21】

一種治療罹患非典型低血糖症之患者之方法，該方法包含以有效提高血糖水平之量向有需要之患者投與如請求項20之醫藥組合物的步驟。

【發明圖式】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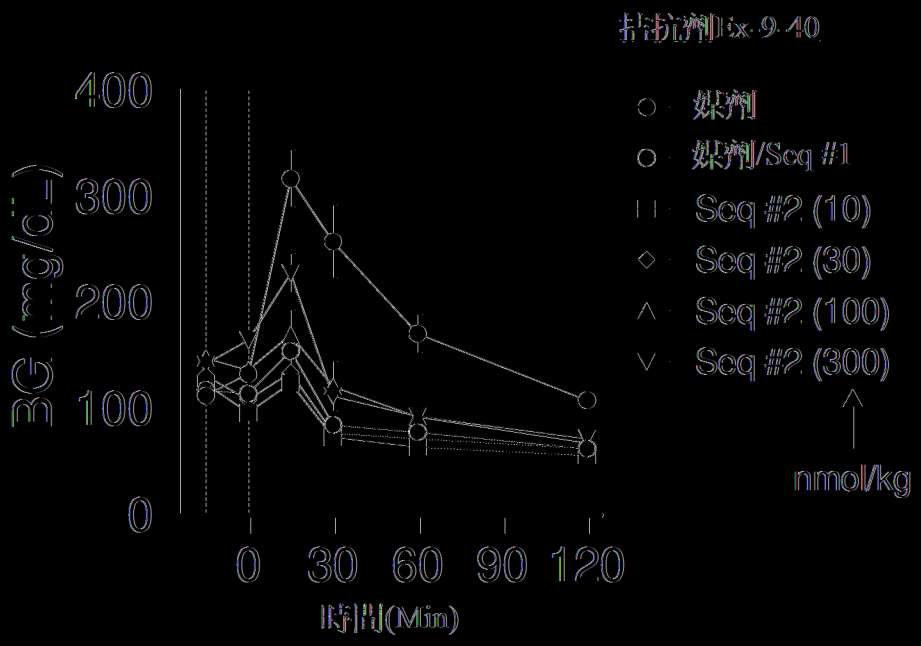
300
200
100
0
-100
ΔBG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
媒劑/Seq #1
Seq #16 (10)
Seq #16 (30)
Seq #16 (100)
Seq #16 (300)
nmol/kg

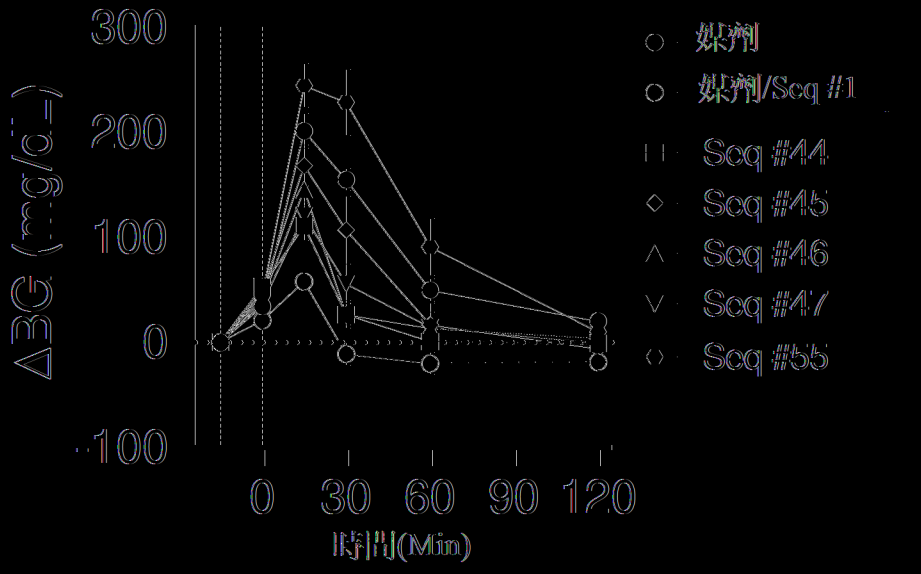
【圖1】


MBX非特異劑
400
300
200
100
0
BG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
媒劑/Seq #1
Seq #16 (10)
Seq #16 (30)
Seq #16 (100)
Seq #16 (300)
nmol/kg

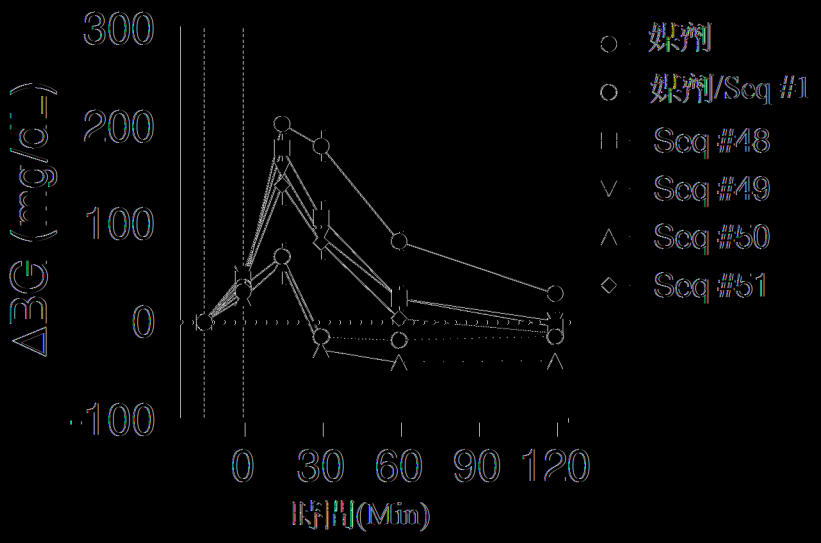
【圖2A】


拮抗劑Ex.9.40
400
300
200
100
0
BG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
媒劑/Scq #1
Scq #2 (10)
Scq #2 (30)
Scq #2 (100)
Scq #2 (300)
nmol/kg

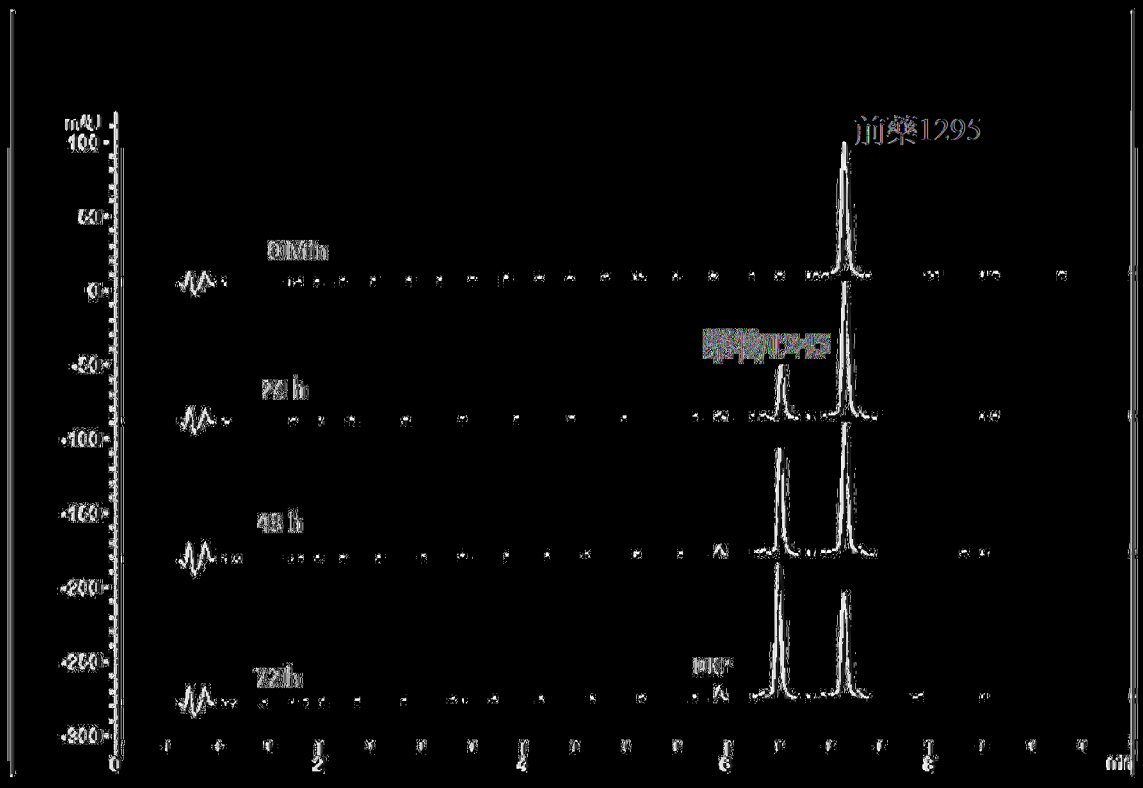
|(圖2B)|


300
200
100
0
-100
ΔBG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
媒劑/Scq #1
Scq #44
Scq #45
Scq #46
Scq #47
Scq #55

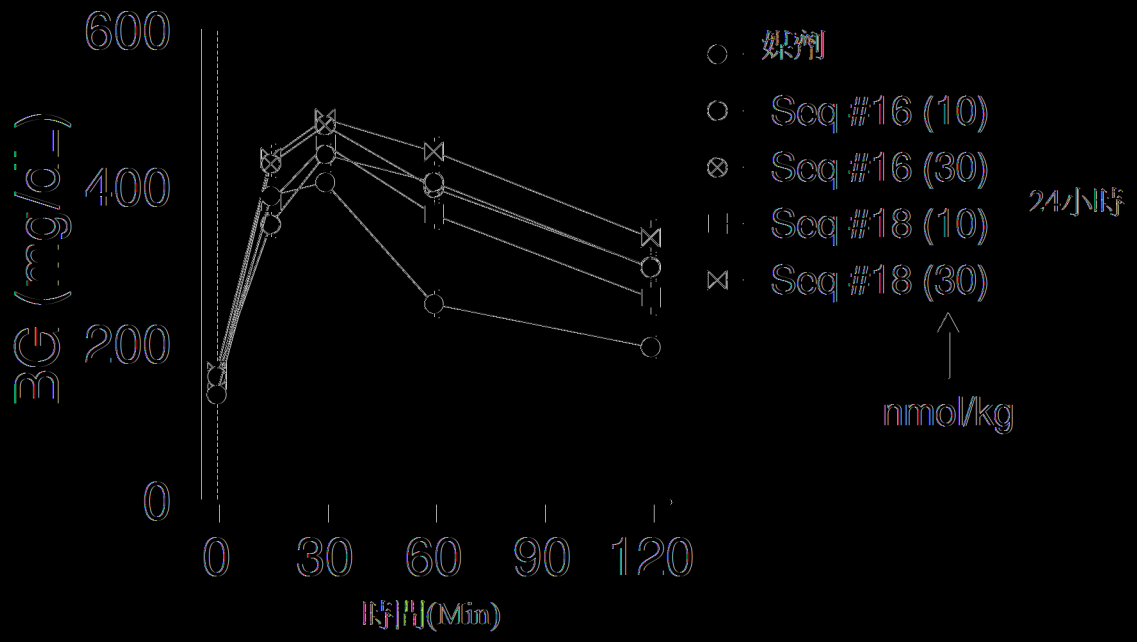
|(圖3)|


300
200
100
0
-100
ΔBG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
媒劑/Seq #1
Seq #48
Seq #49
Seq #50
Seq #51

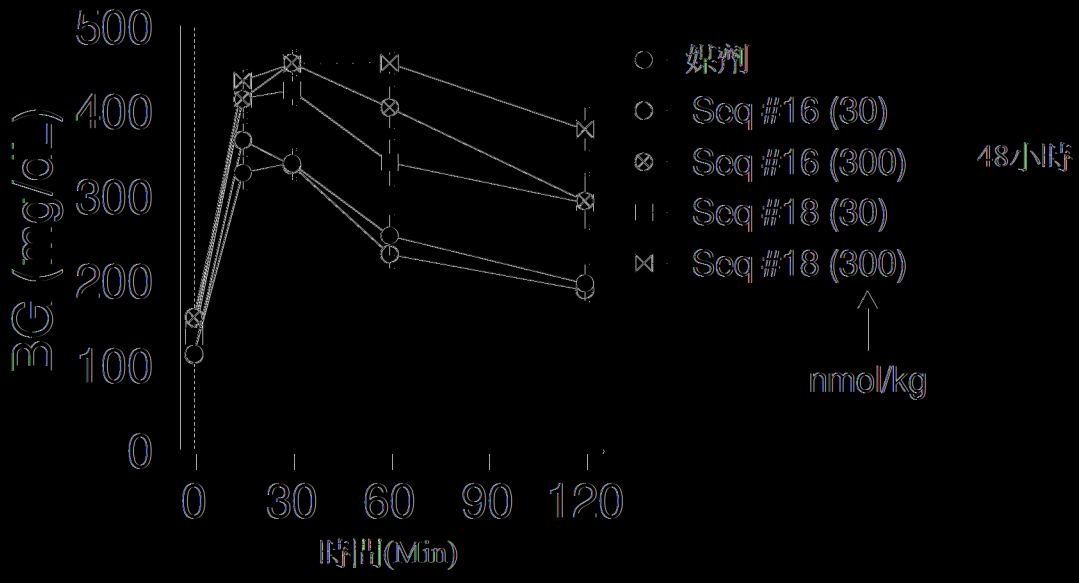
|(圖4)|


前藥1295
0Min
48 h
72 h
mAU
100
50
0
-50
-100
-150
-200
-250
-300
0
2
4
6
8
min

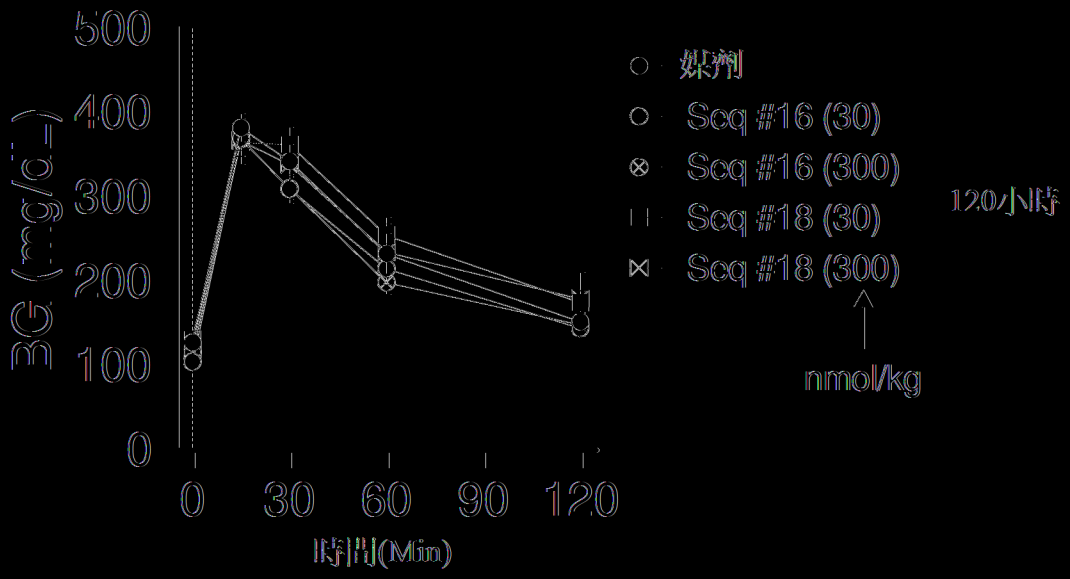
|(圖5A)|


600
400
200
0
BG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
Scq #16 (10)
Scq #16 (30)
Scq #18 (10)
Scq #18 (30)
24小時
nmol/kg

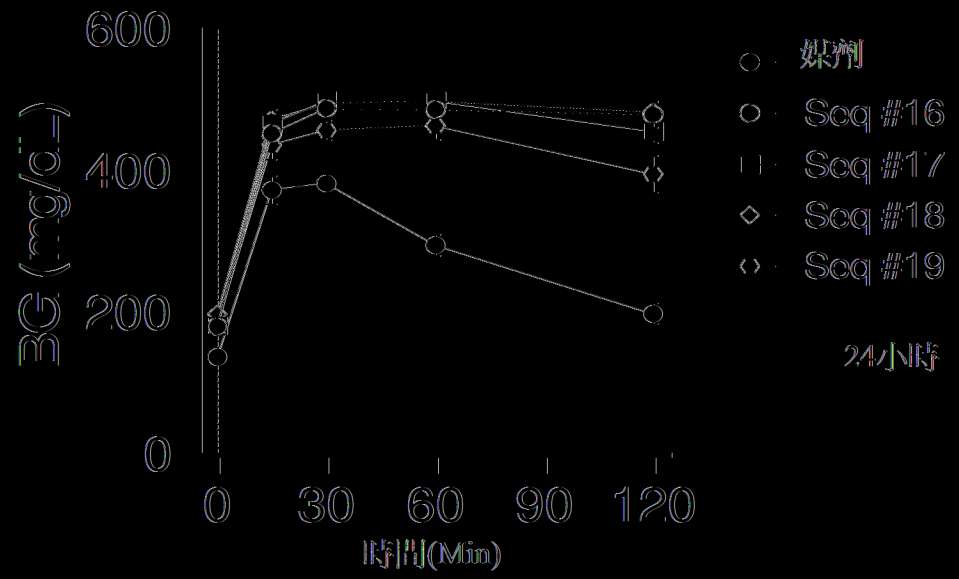
|(圖5B)|


500
400
300
200
100
0
BG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
Scq #16 (30)
Scq #16 (300)
Scq #18 (30)
Scq #18 (300)
48小時
nmol/kg

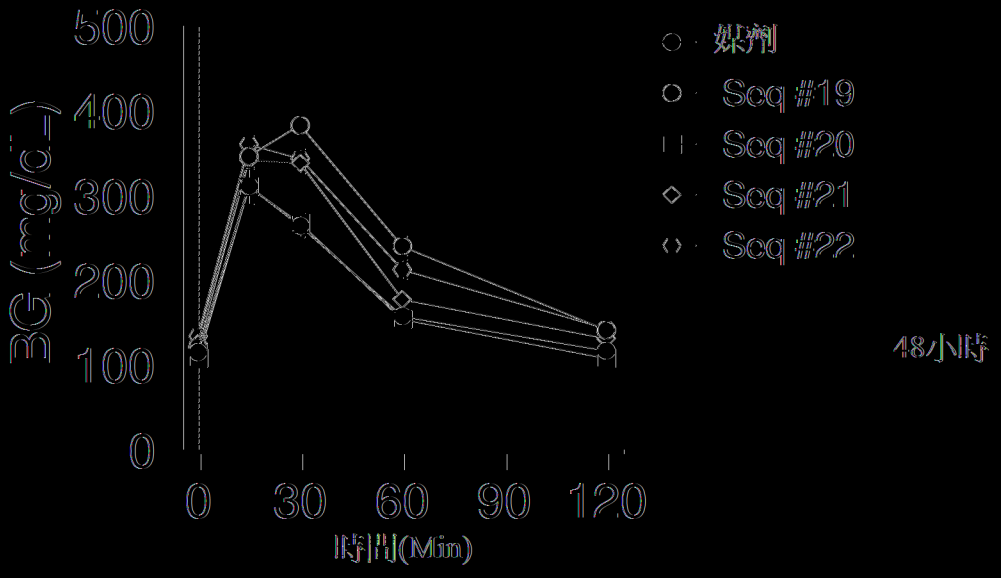
|(圖5C)|


500
400
300
200
100
0
BG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
Scq #16 (30)
Scq #16 (300)
Scq #18 (30)
Scq #18 (300)
120小時
nmol/kg

|(圖5D)|


600
400
200
0
BG (mg/dL)
0
30
60
90
120
時間(Min)
媒劑
Scq #16
Scq #17
Scq #18
Scq #19
24小時

|(圖6A)|



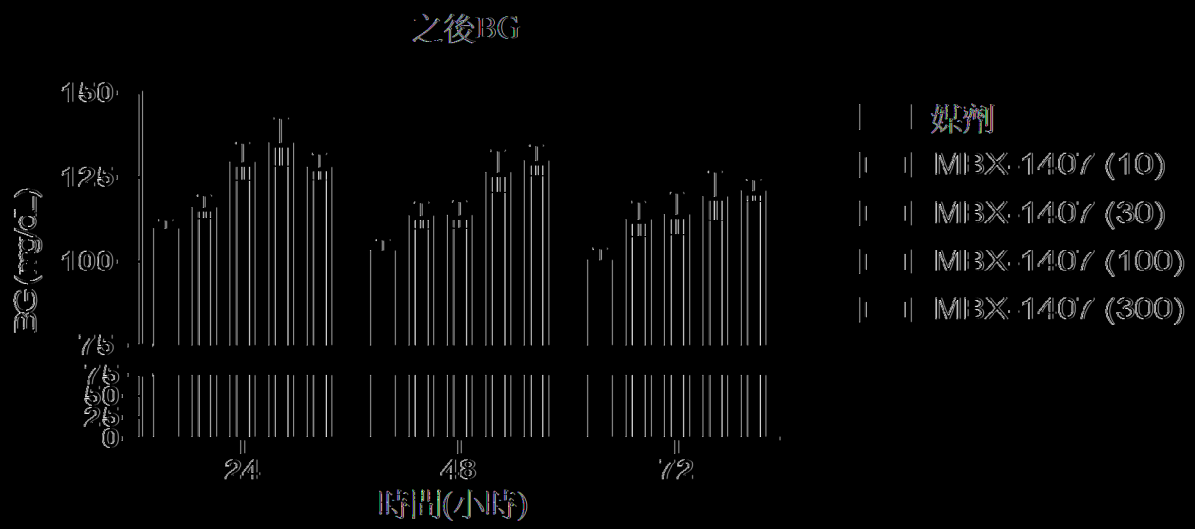
|(圖6B)|

N端指防 醯化GLP-1拮抗劑

MBX-1391:	X/ZGDVSSYLEEQAVREFIEWLVKGGPSSGAPPPSB-		
MBX-1401:	X- DVSRYLEEQAVREFIEWLVRGGPSSGAPPPSO-		
MBX-1402:	X- EVSRYLEEQAVREFIEWLVRGGPSSGAPPPSO-		
MBX-1403:	X- DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSO-		
MBX-1404:	X- DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSO-		
MBX-1406:	X- DVSSYLEEQAVREFIAWLVKGGPSSGAPPPSO-		
MBX-1407:	X- DVSSYLEEQAVREFIAWLVRGGPSSGAPPPSO-		
MBX-1408:	X- DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSO-		
MBX-1416:	X- DVSSYLEEQAVREFIAWLVRGGPSSGAPPPS-		

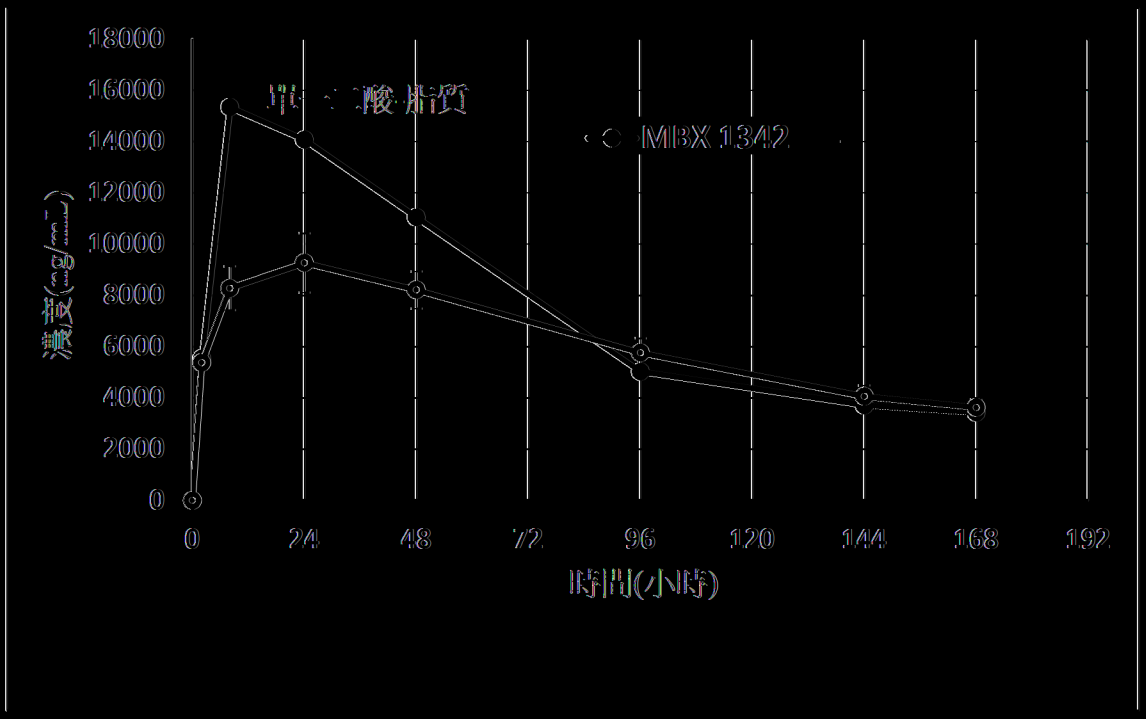
X-C18-1酸　　K-rF-miniPEG　　O-K(C18-1酸)　　B-K(miniPEG-rF-C16-甲酸)

|(圖7)|



1407	XDVSSYLEEQAVREFTAWLVRGGPSSGAPPPSO	酸	580nM

(圖8)

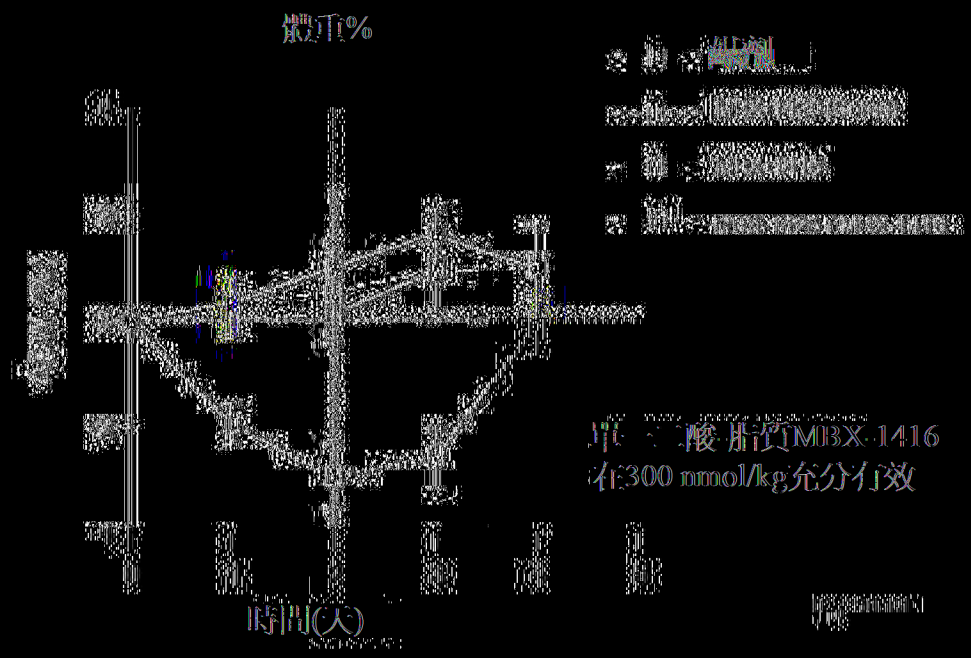


(圖9)

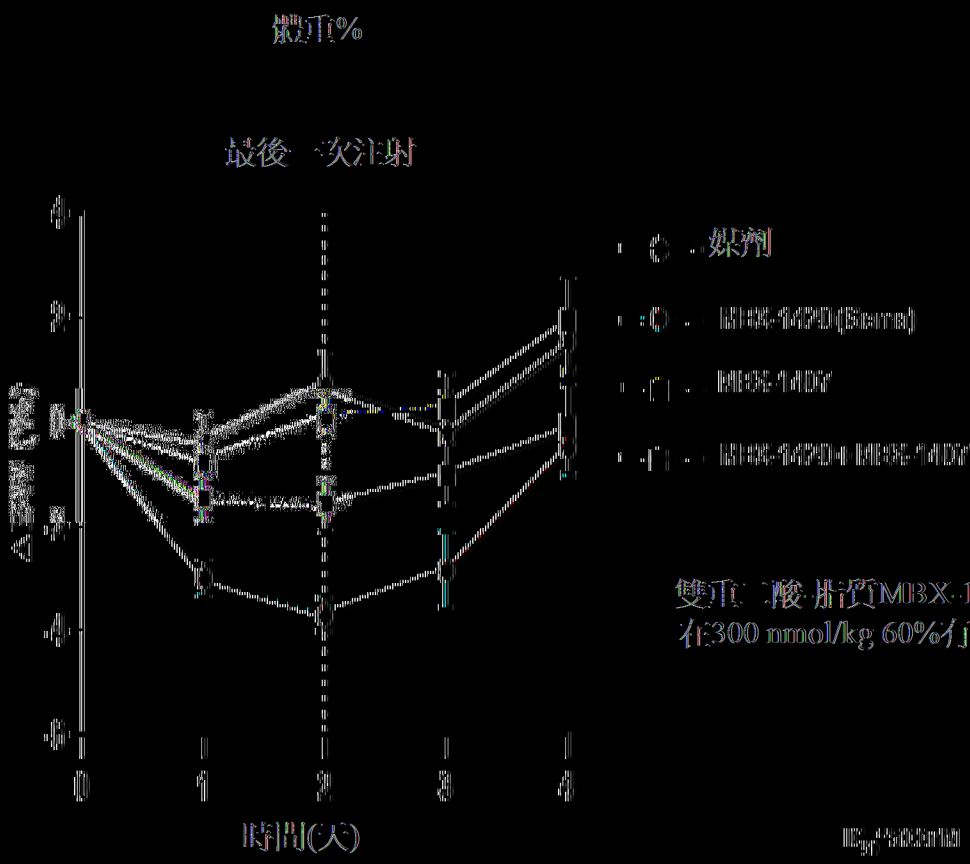
			IC_{50} nM
1342		DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPSO-醯胺	41
1373	k (X) G	DLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-醯胺	14
1416	X	DVSSYLEEQAVREFIAWLVRGGPSSGAPPPS-酸	36
1417	ZK (X) G	DVSSYLEEQAVREFIAWLVRGGPSSGAPPPS-酸	80
1418	Z	DVSSYLEEQAVREFIAWLVRGGPSSGAPPPSO-酸	67

Z-焦麩醯胺酸　　X-C18-二酸　　O-K(C18-二酸)

(圖10)

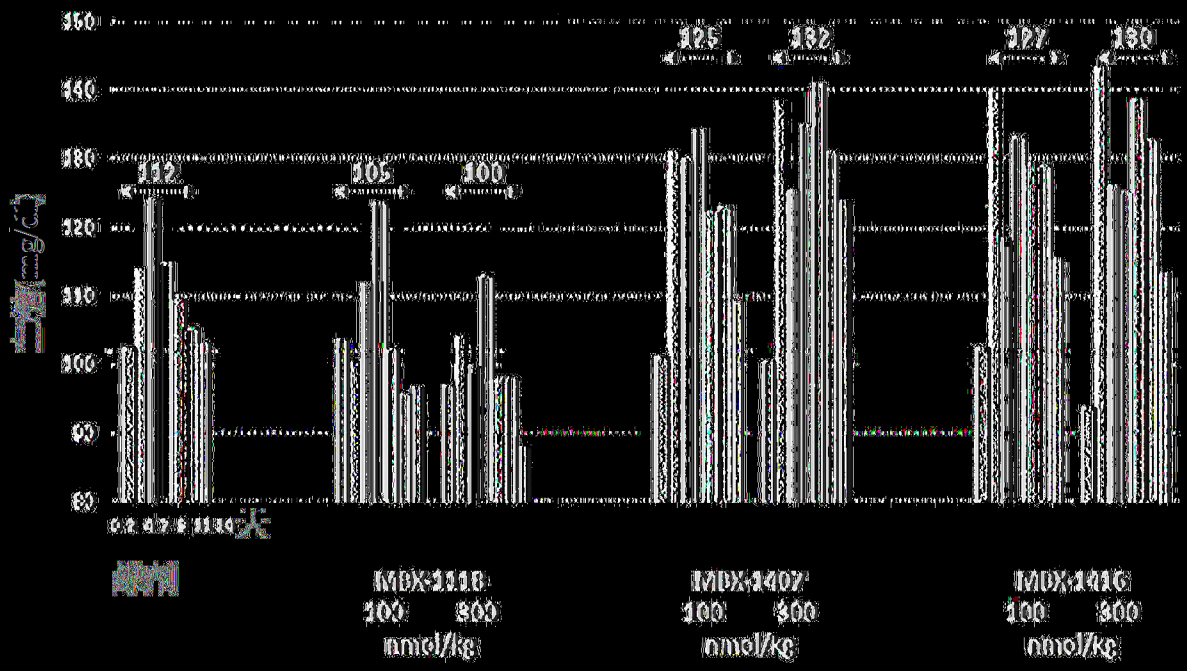


|(圖11A)|

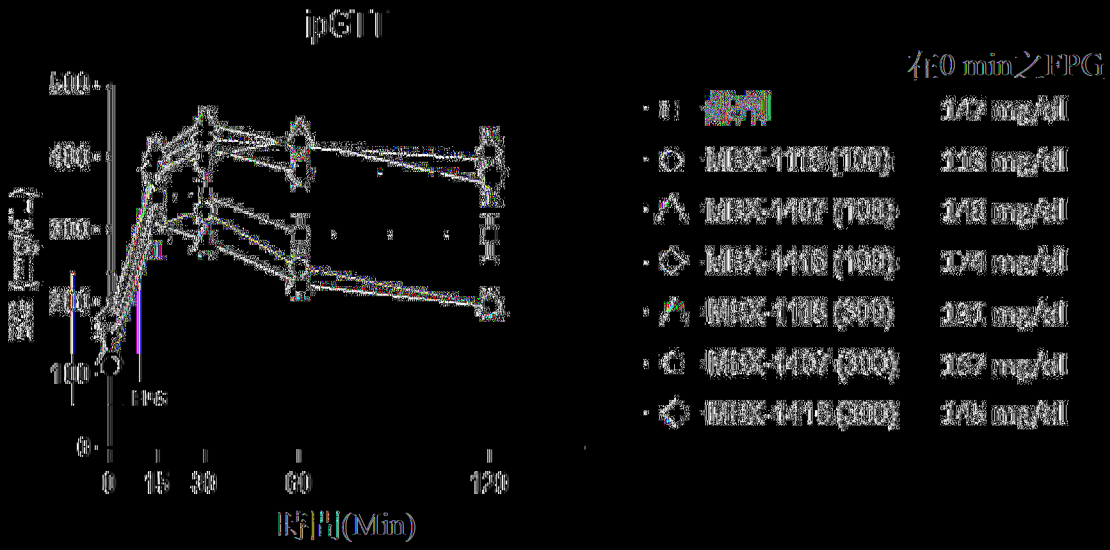


雙重二酸肽MBX-1407
在300 nmol/kg 60%有效

|(圖11B)|


160
140
120
100
80
112
105
100
125
132
127
130
MBX-1118
MBX-1407
MBX-1416
100 300
100 300
100 300
nmol/kg
nmol/kg
nmol/kg

(圖12)


ipGTT
在0 min之FPG
500
400
300
200
100
0
0
15
30
60
120
時間(Min)
142 mg/dl
116 mg/dl
148 mg/dl
174 mg/dl
131 mg/dl
167 mg/dl
145 mg/dl

[圖13]