様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

令和　元 年　 ６ 月 １７ 日現在

機関番号：８２４０１
研究種目：基盤研究(C)（一般）
研究期間：2016～2018
課題番号：１６Ｋ０８２５９

研究課題名（和文）First neuronal guidance lipid: Elucidation of biosynthesis and development of lead compounds to support neuronal recovery after injury

研究課題名（英文）First neuronal guidance lipid: Elucidation of biosynthesis and development of lead compounds to support neuronal recovery after injury

研究代表者

ＧＲＥＩＭＥＬ　ＰＥＴＥＲ（Greimel, Peter）

国立研究開発法人理化学研究所・脳神経科学研究センター・専任研究員

研究者番号：６０５２５５４１

交付決定額（研究期間全体）：（直接経費）　　3,700,000円

研究成果の概要（和文）：リゾ脂質－ＧＰＲ５５相互作用を特徴づけるために、ＧＰＲ５５の新規相同性モデルを作成した。 LysoPtdGlcおよびアシル鎖上およびリン酸部分上の修飾を特徴とする選択された類似体への合成アクセスが確立された。 各合成脂質の生物学的活性を評価した。 分子動力学シミュレーションを行った。 シミュレーション結果と生物学的実験との組み合わせは、ＧＰＲ５５の潜在的なリガンド進入口および結合ポケットの詳細への洞察を提供した。 これらの結果は、グルコシルイノシトール立体配置頭部基およびGPR55活性化のためのアシル鎖長の要件に対する優先性を強調している。

研究成果の学術的意義や社会的意義
Detailed characterization of the GPR55 ligand binding pocket is an essential per-requisite for rational design of novel GPR55 specific antagonists, which have a high potential to be applied in neuropathic pain relieve treatments in the future.

研究成果の概要（英文）：To characterize lysolipid-GPR55 interaction a novel homology model of GPR55 was created. Synthetic access to LysoPtdGlc and selected analogues featuring modifications on the acyl chain and on the phosphate moiety were established. The biological activity of each synthetic lipid was assessed using a GPR55-dependent chemotropism assay in primary sensory neurons. Molecular dynamics simulations of the GPR55 homology model in presence of synthetic lysolipid ligands have been performed and assessed. Combination of the molecular dynamics simulations and biological experiments provided insight into the potential ligand entry port and binding pocket specifics of GPR55. These results highlight the preference for gluco- over inositol- and galacto-configured headgroups. Furthermore, the specific acyl chain length required for GPR55 activation has been determined and is in good agreement with the created homology model of GPR55.

研究分野：Organic Synthesis

キーワード：Phosphatidylglucoside　GPCR　Lipids　GPR55

様　式　C－１９、F－１９－１、Z－１９、CK－１９（共通）

１．研究開始当初の背景

In 2003 phosphatidyl-ß-D-glucoside (PtdGlc) - the precursor of lyso-PtdGlc - was isolated from mammalian sources for the first time. It is comprised of a ß-glucoside linked to a phosphatidic acid (PA) residue [*Tetrahedron Lett.* 2008]. Interestingly, the fatty acid pattern of the PA residue consists exclusively of saturated fatty acids, namely arachidic acid (C20:0) at the secondary hydroxy function and stearic acid (C18:0) at the primary hydroxy function. Furthermore, natural PtdGlc exists as a mixture of both stereoisomers at the glycerol backbone, raising the intriguing question of its biosynthetic pathway. PtdGlc can be selectively visualized by DIM21, a highly specific AB against PtdGlc [*Bioorg. Med. Chem.* 2008].
We reported [*Science*, 2015] that the soluble form of PtdGlc, termed lyso-PtdGlc, is released from glial cells by secretory PLA_2 in the central nervous system to guide neuronal growth during development. After birth, production of PtdGlc completely ceases. Interestingly, while a directed gradient of lyso-PtdGlc resulted in axonal outgrowth repulsion, engulfing the growth cone of neurons in lyso-PtdGlc (10μM) resulted in growth cone collapse, thus terminating neuronal growth.

２．研究の目的

We reported [*Science* 2015] the fist lipid molecule, called lyso-PtdGlc, capable of guiding and terminating neuronal growth. The recently identified receptor for lyso-PtdGlc, GPR55, is involved in neurpathic pain sensation. The aim of this project is: 1) to characterize the ligand binding pocket of GPR55; **2**) to identify lead compounds with GPR55 agonistic and antagonistic activity for drug development.

３．研究の方法

A novel homology model of GPR55 will be developed. The validity of the GPR55 homology model will be assessed by comparison with biological assay results of synthetic GPR55 agonists and antagonists.

４．研究成果

To characterize lysolipid-GPR55 interaction a novel homology model of GPR55 was created. Synthetic access to LysoPtdGlc and selected analogues featuring modifications on the acyl chain and on the phosphate moiety were established. The biological activity of each synthetic lipid was assessed using a GPR55-dependent chemotropism assay in primary sensory neurons. Molecular dynamics simulations of the GPR55 homology model in presence of synthetic lysolipid ligands have been performed and assessed. Combination of the molecular dynamics simulations and biological experiments provided insight into the potential ligand entry port and binding pocket specifics of GPR55. These results highlight the preference for gluco- over inositol- and galacto-configured headgroups. Furthermore, the specific acyl chain length required for GPR55 activation has been determined and is in good agreement with the created homology model of GPR55.

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〔図書〕（計　　件）

〔産業財産権〕
○出願状況（計　　件）

名称：

発明者：
権利者：
種類：
番号：
出願年：
国内外の別：

○取得状況（計　　件）

名称：
発明者：
権利者：
種類：
番号：
取得年：
国内外の別：

〔その他〕
ホームページ等

６．研究組織

(1)研究分担者
研究分担者氏名：
ローマ字氏名：
所属研究機関名：
部局名：
職名：
研究者番号（8 桁）：

(2)研究協力者
研究協力者氏名：
ローマ字氏名：

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