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研究課題名(和文) 新規脳分子による新しい生殖制御機構の解明

研究課題名(英文) Novel Mechanisms of the Regulation of Reproduction by Novel Brain Hormones

研究代表者

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研究成果の概要(和文)：

我々は新規脳ホルモンである生殖腺刺激ホルモン放出抑制ホルモン(gonadotropin-inhibitory hormone; GnIH)を鳥類から発見した。本研究では、GnIHはヒトなどの霊長類から無顎類に至る全ての脊椎動物に存在することを明らかにした。さらに、GnIHは生殖腺刺激ホルモンの合成と放出を抑制して生殖腺の発達と機能を抑える働きがあることを明らかにした。本研究により、この新規脳分子による新しい生殖制御機構の大略が解明された。

研究成果の概要(英文)：

We discovered a novel avian hypothalamic neuropeptide inhibiting gonadotropin release, named gonadotropin-inhibitory hormone (GnIH). We demonstrated that GnIH acts on gonadotropes and GnRH neurons via GPR147 to inhibit gonadal development and maintenance by decreasing gonadotropin release and synthesis. We further demonstrated that GnIH has an evolutionarily conserved role in controlling reproduction across vertebrate species.

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キーワード：視床下部ホルモン・脳下垂体ホルモン・発現制御・シグナル伝達・生殖

1. 研究開始当初の背景

1970年代に哺乳類から生殖腺刺激ホルモンの放出を促進する生殖腺刺激ホルモン放出ホルモン(GnRH)が発見されて以来、脊椎動物の生殖腺の発達と機能はこの古典的脳ホルモンであるGnRHに支配されていると考えられてきた。一方、生殖腺刺激ホルモンの放出を抑制する脳ホルモンの存在は長く不明であった。2000年に、我々は生殖腺刺激ホルモンの放出を抑制する新規の脳ホルモンを鳥類のウズラから発見して、生殖腺刺激ホルモン放出抑制ホルモン(GnIH)と名付けた。

2. 研究の目的

GnIHによる新しい生殖制御機構の解明に

は、ヒトを含めた他の脊椎動物からGnIH同族ペプチドを同定する必要がある。本研究の目的は、脊椎動物に広く存在すると考えられるGnIHとGnIH同族ペプチドを同定し、これらの新規脳分子による新しい生殖制御機構を解明することである。

3. 研究の方法

(1) 霊長類から魚類、無顎類に至る脊椎動物の脳から高速液体クロマトグラフと質量分析によりGnIH同族ペプチドを同定し、GnIHとGnIH同族ペプチドの起源と構造の分子進化を解析した。
(2) GnIHと新たに同定したGnIH同族ペプチドの生殖腺の発達と機能における

生理作用を解析した。

(3) GnIHとGnIH同族ペプチドの受容体を同定して、これらの新規脳分子の作用機構を解析した。

(4) GnIHとGnIH同族ペプチドの発現を制御する脳分子を同定して、これらの新規脳分子の発現制御機構を解析した。

4. 研究成果

以下の新規の重要な研究成果が得られた。

(1) 霊長類（ヒトとサル）、哺乳類（ヒツジ、ハムスター、ラットなど）、鳥類（ムクドリ、キンカチョウなど）、両生類（カエルとイモリ）、魚類（キンギョ、サケなど）、無顎類（ヌタウナギとヤツメウナギ）の脳からGnIHとGnIH同族ペプチドを同定して、GnIHとGnIH同族ペプチドはC-末端側に共通構造を持つことやこれら新規脳分子の起源は無顎類に遡ることを明らかにした。

(2) GnIHとGnIH同族ペプチドは脳下垂体の生殖腺刺激ホルモン産生細胞と視床下部のGnRHニューロンに作用して生殖腺刺激ホルモンの合成と放出を抑制することを明らかにした。

(3) GnIHとGnIH同族ペプチドは生殖腺刺激ホルモンの合成と放出を抑制して生殖腺の発達と機能を抑える働きがあることを明らかにした。

(4) GnIHとGnIH同族ペプチドの発現を松果体と目の網膜で作られるメラトニンが誘導することを明らかにした。

以上の研究成果はこれまでの常識を覆すものであり、新規脳分子であるGnIHとGnIH同族ペプチドによる新しい生殖制御機構の大略が解明された。研究成果の多くは関連研究分野のトップジャーナルに掲載され、多数の国際会議における基調・招待講演により多くのインパクトを与えた。今後は、GnIHの作用機構のより詳細な基礎研究と生殖機能障害に対する新しい治療薬の開発に向けた応用研究が期待される。

5. 主な発表論文等

（研究代表者、研究分担者及び連携研究者には下線）

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[産業財産権]

○出願状況 (計 1 件)

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