New Hormone Analogs for Treating Hypoparathyroidism

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Technology description

G protein-coupled receptors (GPCRs) are the targets of many current therapeutic agents. As they can adopt multiple activated states, there is increasing interest in synthetic molecules that display altered receptor-state selectivity patterns relative to natural agonists. Receptor state-selective agonists are highly prized because these molecules can serve as powerful tools for elucidating signal-transduction mechanisms, and they may give rise to therapeutic agents with minimal deleterious side effects. At present, there is no way to design such agonists via rational methods.

The parathyroid hormone receptor-1 (PTHR1) is a GPCR that plays a key role in regulating several important physiological functions. Its agonists, including PTH(1-34) (the active ingredient in the drug teriparatide), are used to treat osteoporosis and potentially hypoparathyroidism. Hypoparathyroidism is the underproduction of parathyroid hormone, leading to low levels of calcium in the blood and serious symptoms. Chronic hypoparathyroidism is conventionally treated with vitamin D analogs and calcium supplementation. However, such treatments are contraindicated in many patients due to potential renal damage. UW–Madison researchers have developed backbone-modified analogs of PTH(1-34). The analogs exhibit advantageous properties; they are biased toward Gs activation/cAMP production relative to β arrestin recruitment.

The analogs were generated via an unconventional strategy in which the backbone of a natural PTHR-1 agonist was altered, rather than the side-chain complement. More specifically, selected α-amino acid residues were systemically replaced with either β-amino acid residues or with unnatural D-stereoisomer α-amino acid residues.

The researchers have shown that backbone-modification can rapidly identify potent agonists with divergent receptor-state selectivity patterns relative to a prototype peptide.
The Wisconsin Alumni Research Foundation (WARF) is seeking commercial partners interested in developing non-natural analogs of parathyroid hormone (1-34) that function as agonists of the parathyroid hormone receptor-1 and display modified activity profiles. The new analogs may be useful in pharmaceuticals for treating hypoparathyroidism.

Application area

Therapeutic peptides for treatment of hypoparathyroidism

Advantages

Exhibit biased agonist properties
Improved proteolytic stability
Enhanced target selectivity

Institution

Wisconsin Alumni Research Foundation

Inventors

Shi Liu
Samuel Gellman

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com