



Applications

- A potential therapeutic for osteoporosis
- A tool for designing selective PTH1R-binding molecules

Benefits

- Highly selective and effective
- Potentially fewer negative side effects than teriparatide

VARI IP-00094

Patent Status: Pending
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Parathyroid Hormone (PTH) and PTH-Related Protein (PTHrP) Peptides

Innovative peptides that bind and activate the PTH/PTHrP receptor (PTH1R).

Background

Osteoporosis affects more than 10 million people in the United States. The disease is characterized by decreases in bone mass and density, which can lead to an increased chance of fractures, particularly in the hip and vertebrae. A common treatment option is parathyroid hormone (teriparatide, or Forteo). While teriparatide is effective at treating osteoporosis, there is the potential for adverse side effects in some individuals resulting from the undesirable activation of the PTH/PTHrP receptor (PTH1R).

Technology

Van Andel Research Institute (VARI) scientists have generated a high-resolution crystal structure of PTHrP bound to the extracellular domain (ECD) of PTH1R and compared it to the PTH-PTH1R ECD complex. The receptor accommodates different binding modes by changing the conformation of two residues at the peptide binding site. Guided by the structures, the researchers designed hybrid peptides containing interchanged PTH and PTHrP residues at positions that determine the different binding modes. VARI scientists used the PTH- and PTHrP-bound structures as a guide to design PTH and PTHrP peptide analogs—some of which are hybrid PTH/PTHrP peptides—allowing them to obtain RG-selective peptides that strongly stimulate cAMP signaling with temporally shorter responses. These analogs may have therapeutic potential as more purely anabolic PTH analogs lacking hypercalcemic side effects by providing a potent, but pulsatile action at the receptor.

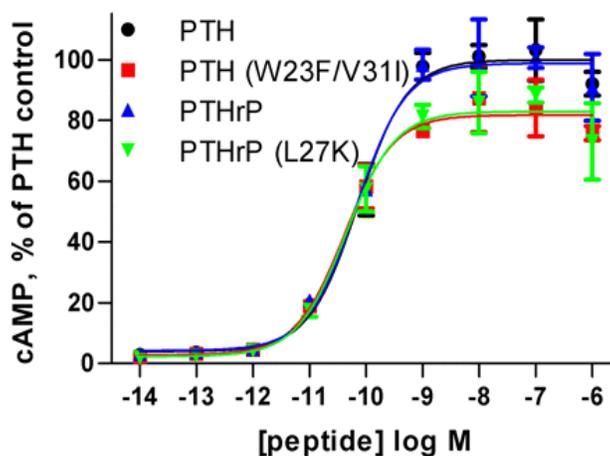


Figure 1: Stimulation of cAMP signaling by hybrid PTH/PTHrP(1–34)NH₂ peptides. Cells transiently expressing PTH1R were stimulated with the indicated peptides for 30 minutes at 37°C. Data are normalized to the maximum cAMP level observed in the presence of PTH(1–34) for which basal cAMP was 0.24 pmol per well and maximal cAMP was 6.1 pmol per well. The EC₅₀ values for PTH, PTH(W23'F/V31'I), PTHrP, and PTHrP(L27'K) were 72, 42, 68, and 44 pm, respectively.

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