Pulsatile Release of PTH for Osteoporosis Treatment

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Introduction

Parathyroid hormone (PTH) is the major hormone regulating calcium metabolism and is involved in both catabolic and anabolic actions on bone. Whereas continuous exposure to PTH results in bone resorption, administration at intermittent doses results in bone formation by increasing osteoblast number and activity. This anabolic feature of PTH makes it a particularly appealing treatment for patients with osteoporosis. However, effective therapy of osteoporosis currently involves daily or twice daily subcutaneous injections of PTH, which is costly and inconvenient. In this study, we designed and fabricated a controlled release device to administrate PTH pulsatile delivery. The device has a laminate structure composed of polyanhydrides as isolation layers and biocompatible alginate as drug-loaded layers. The bioactivity of released PTH was examined *in vitro* after initial release.

Methods

Polyanhydrides were synthesized and characterized by NMR, GPC and FTIR. The surface erosion character of polyanhydrides was observed by scanning electron microscopy (SEM). The concentration of PTH in the release medium was measured using PTH (1-34) ELISA kit. The *in vitro* bioactivity of released PTH was determined by adenylate cyclase stimulation assay and cAMP binding protein assay.

Results and Discussion

Polyanhydrides with three components of sebacic acid, 1,3-bis(*p*-carboxyphenoxy) propane and poly(ethylene glycol) (PEG) were synthesized by melt polymerization. PEG segments were incorporated into polyanhydrides to adjust the erosion rate of polyanhydrides and to improve process property of polyanhydride films.

The pulsatile protein delivery device was fabricated using a layer-by-layer technique. The released pattern of the laminate device was first investigated using bovine serum albumin (BSA) as a model protein. Four separated pulses with almost the same of amount of BSA for each pulse were obtained (Figure 1). The lag time among each pulse could be easily controlled by the thickness of polyanhydride films, which act as isolation layers.

The pulsatile release of PTH from the laminated device was also achieved, and the bioactivity of PTH released from each layer was measured. Similar amount of PTH was released from each layer. The high level expression of cAMP showed that the released PTH from each layer retained high bioactivity (Figure 2).

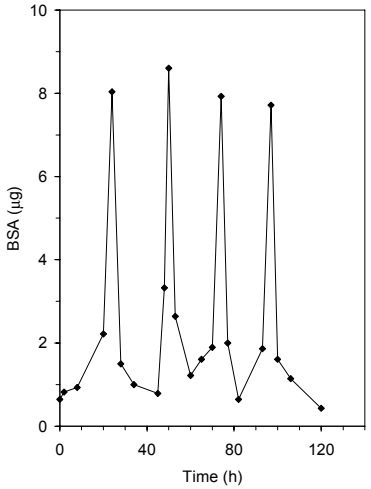

Figure 1. Pulsed release profile of BSA from the laminated device. Four layers of BSA (each layer includes 9 μg BSA) were loaded into the device. The thickness of polyanhydride films is about 150 μm.

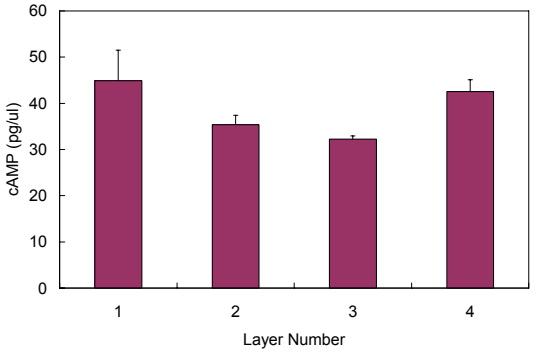

Figure 2. Biologic activity of PTH released from the laminated device (Four layers of PTH were loaded into the device). The released PTH of each layer were 13.8±6.4, 6.7±1.2, 5.1±0.3, and 11.9±2.2 pM, respectively.

Conclusions

A laminated device using polyanhydrides as isolation layers was designed and fabricated to delivery PTH in a pulsatile manner. The released PTH retained high bioactivity, which implicates the potential application of this device for clinical osteoporosis treatment.

References

[1] Grayson A.R. et.al. *Nat. Mater.* 2:767-772, (2003)
[2] Wei G. et.al. *Biomaterials. 25*:345-352, (2004)