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NEWS

The two faces of PTH: exploring parathyroid hormone and its role in bone

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Webinar: Development of PTH and PTHrP analogs with new therapeutic potentials.

Levels of calcium, phosphate and other compounds important for the function of the skeleton are carefully regulated in the human body. One, if not the most important regulator, is parathyroid hormone or PTH.

PTH acts on cells via two specific receptors, the PTH1 and PTH2 receptor. In bone and kidney, the major receptor responsible for PTH action is the PTH1 receptor. Alterations in PTH function have been linked to several diseases, including osteoporosis, renal failure and hyper- and hypoparathyroidism. Therefore, studies that help to understand more about PTH and its receptors could help scientists develop new therapies.

Dr Thomas Gardella and colleagues at Massachusetts General Hospital in Boston are investigating the PTH and the PTH1 receptor and searching for new PTH analogs with the aim of developing drugs that treat PTH-related conditions.[1] He discusses the work of his team and others in this webinar—http://www.nature.com/bonekey/webinars/index.html?key=webinar33.

One of the long-standing puzzles in the field is that PTH has opposite effects on bone. When PTH levels fluctuate, bone is more likely to be formed; whereas continuous PTH levels cause bone loss. This paradigm is why PTH is considered a useful potential therapy for both osteoporosis, where bone formation is needed, and hypoparathyroidism, which causes a deficit of calcium.

Scientists have a very clear idea about the structure of PTH and the PTH1 receptor. The receptor exists in two different conformations, which affects what molecules—or ligands—bind to it. Different potential drug molecules prefer different receptor conformations.[2] Dr Gardella and his team have found that one particular ligand, M-PTH(1–34), when attached to a certain conformation of the PTH receptor, known as R^0, can activate the receptor very strongly—more so than regular PTH. This conformation/ligand combination boosts the level of calcium in the blood above and beyond that of native PTH.

Compounds like M-PTH(1–34) that are selective for the R^0 conformation, are therefore candidates for the treatment of hypoparathyroidism, a relatively rare disorder affecting some 60 000 patients in the United States. Current treatments are limited to large doses of calcium and vitamin D, which have the risk of kidney damage.

Other research teams have already treated hypoparathyroidism patients with PTH injections,[3] but these only boost calcium levels for a few hours. Dr Gardella's team has developed and utilized several PTH analogs, including LA-PTH, which is similar to M-PTH(1–34) in that it is selective for the R^0 confirmation. So far, LA-PTH has worked well in mice and monkeys,[4,5] and the team is anticipating an application to the Food and Drug Administration to test the compound in humans in the near future.

Ongoing research suggests that a deeper understanding of PTH–PTH receptor interactions could improve the treatment of osteoporosis as well. Intermittent injection of PTH(1–34) is already approved as a treatment for postmenopausal osteoporosis, and one candidate molecule, BA058 (also known as abaloparatide), is in late-stage clinical testing by Radius Health Company, based in Cambridge, Massachusetts (see Radius' Publications page for details). Dr Gardella's team examined BA058 to determine the mechanism of interaction with the receptor and demonstrated that it interacts with a different conformation of the PTH receptor, called RG.[6] This results in an intermittent signal, which favours bone formation.

Finally, Dr Gardella presented new insights into the concept of developing more easily administered treatments for disorders involving altered PTH levels. The overall goal is to develop small molecules that can interact with the PTH1 receptor like native PTH. Such molecules have so far proved elusive, but Dr Gardella is optimistic that they will be discovered.

For more details on PTH, its receptor and using PTH analogs to treat PTH disorders, watch the accompanying webinar at http://www.nature.com/bonekey/webinars/index.html?key=webinar33.

Edited by LJ Suva

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