

Summary – Calcium Receptors: Potential targets for novel treatments for skeletal disease

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The final session at this year's Sun Valley Workshop covered a topic that last appeared on the agenda in 1994. At that time, I presented an overview of the pharmacology of the calcium receptor, John Fox covered the pre-clinical data on the first calcimimetic for hyperparathyroidism (NPS R-568, which was already in the clinic), and Scott Miller described some experiments that we did to ascertain the feasibility of using calcilytics for treating osteoporosis. Just nine months prior to our little session on "Ca²⁺ Receptors and Metabolic Bone Disorders," Ed Brown and Steve Hebert had reported the cloning of the Ca²⁺ receptor, so we finally had some insight into the structure of our target receptor. It was a rather heady time and we had some optimistic yet reasonable expectations about the future. We believed a calcimimetic compound could be a first in class pharmaceutical for treating hyperparathyroidism. As we already had plenty of calcimimetic compounds, we expected, using the cloned receptor in a high-throughput screening mode, to now discover an equally large number of calcilytic compounds. We also expected to learn if the Ca²⁺ receptor is expressed in the cellular elements of bone and we hoped to achieve some mechanistic understanding of how skeletal tissues respond to changes in the concentration of extracellular Ca²⁺. A decade later, we see that only some of these expectations have been fulfilled.

The four presentations comprising the 2004 session on Ca²⁺ receptors were ordered with the intent of moving from bench to bedside, from controversy to certainty. **Wenhan Chang** (University of California, San Francisco) led off with a summary of his more recent work on the localization and possible function of the Ca²⁺ receptor in cartilage, specifically growth plate cartilage. He used a variety of techniques to convincingly demonstrate the expression and cellular loca-

tion of the Ca²⁺ receptor in the growth plate. Complementing these results were those derived from a series of functional studies, in which he showed that changes in the concentration of extracellular Ca²⁺ affect parameters associated with differentiation of cartilage, such as proteoglycan accumulation. Because these effects of extracellular Ca²⁺ were depressed by anti-sense oligonucleotides to the Ca²⁺ receptor or by overexpression of a dominant-negative mutant of the Ca²⁺ receptor, it seemed reasonable to conclude that they were in fact mediated by the Ca²⁺ receptor. The story became even more intriguing when he presented data linking these effects of extracellular Ca²⁺ to expression of Indian hedgehog and PTHrP; conversely, PTHrP affected responses to extracellular Ca²⁺. Collectively, these various results furnished an elegant story that faltered only when he tried repeating these studies using chondrocytes prepared from Ca²⁺ receptor knockout mice. Given what we know about these cells (they express an alternatively spliced transcript lacking exon 5), they should not have responded to extracellular Ca²⁺, yet they did.

In contrast to this beautiful narrative tarnished by an ugly piece of datum, we have the story in skeletal tissue proper. Not a story, really ... rather a collection of chapters, each using the same characters (PCR, antibodies, pharmacological probes) but providing a different account, not unlike Kurosawa's *Rashomon*. Indeed, a consistent story has never emerged and whether the Ca²⁺ receptor is even expressed (much less what it might be doing) in osteoblasts, osteocytes, and/or osteoclasts remains controversial. **Ed Brown** (Harvard University) did a masterful job of collating all the discrepant findings and provided a very balanced overview of this confusing area. You will have to read his contribution and decide for yourself what you believe. Unfortunately, the levity scattered throughout his presentation is unlikely to come across in the written version.

The potential of these skeletal Ca²⁺ receptors as novel drug targets is thus uncertain. At the outset, we need to reach agreement about its expression and location in skeletal tissues; then can we begin to sort out its functional roles and determine whether it has any therapeutic significance.

The therapeutic potential of the Ca²⁺ receptor expressed

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on parathyroid cells is considerably more certain. There is little question that regulating secretion of parathyroid hormone (PTH) is the primary function of the Ca^{2+} receptor in the body so drugs that target this receptor are effective in regulating circulating levels of endogenous PTH. This was first achieved with activators of the Ca^{2+} receptor (calcimimetics) and was reported the same year the receptor was cloned (at the 1993 ASBMR meeting in Tampa). Antagonists of the Ca^{2+} receptor (calcilytics), however, have been more difficult to discover as recently discussed¹. At this year's Sun Valley Workshop, I filled in for George Stroup (Glaxo SmithKline) who was unable to attend and provided an update on some of these nuances. We have been collaborating on calcilytics for just over a decade now and we are still bothered by some niggling questions. Why is the parathyroid Ca^{2+} receptor so easy to turn on yet so difficult to turn off? Just about every other G protein-coupled receptor, including close relatives like metabotropic glutamate receptors, show just the opposite behavior and it is typically much easier to discover antagonists than agonists. Another unanswered question is why chronic dosing with a calcilytic compound does not cause parathyroid gland hyperplasia, especially since calcimimetics have proven to be so effective at blocking parathyroid cell proliferation in animal models of renal failure. Despite these uncertainties, calcilytic compounds continue to move forward in the clinic.

The final presentation, by **Munro Peacock** (Indiana University), confirmed the optimistic expectations articulated at the first session on Ca^{2+} receptors a decade ago. In March 2004, the calcimimetic compound cinacalcet

(SensiparTM) was approved by the FDA for the treatment of secondary hyperparathyroidism in patients on dialysis and in patients with parathyroid carcinoma. Munro focused specifically on the renal and skeletal effects of this compound seen in these patient populations, many of which can be explained by the resulting changes in circulating levels of PTH. There are, however, some unexpected findings that might result from actions of cinacalcet directly on renal Ca^{2+} receptors. The histomorphometric data on skeletal tissues is still preliminary and no conclusions can yet be made. I believe it is fair to say, however, that the bones of patients with secondary hyperparathyroidism are not getting worse. Indeed, preliminary results from all the clinical trials show that patients on cinacalcet have fewer fractures.

The launch of cinacalcet is the culmination of fourteen years of effort to make a drug that targets the Ca^{2+} receptor. It might well be the last drug that was discovered prior to the cloning of its target receptor. Calcilytic drugs, which stimulate PTH secretion, have a long way to go in the clinic before we will know if the parathyroid Ca^{2+} receptor is also a good target for anabolic therapies for osteoporosis. Even if they fail, there is still some reason to believe that Ca^{2+} receptors in skeletal tissue, should they exist, might provide novel targets for new drugs effective in the treatment of various skeletal diseases.

Reference

1. Nemeth EF. The search for calcium receptor antagonists (calcilytics). *J Mol Endocrinol* 2002; 29:15-21.