Journal of Biomed Research

Eby et al, J Biomed Res. 2022;3(1):1-2.

Commentary

Syndrome similar to Familial Hypocalciuric Hypercalcemia (FHH) produced in mice deleted of the gene encoding transient receptor potential canonical channel 1 (TRPC1)

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Received date: February 08, 2022
Accepted date: February 17, 2022

Citation: Eby B, Lau AK, Pantalia M, Khan U, Lau K. Syndrome similar to Familial Hypocalciuric Hypercalcemia (FHH) produced in mice deleted of the gene encoding transient receptor potential canonical channel 1 (TRPC1). J Biomed Res. 2022;3(1):1-2.

We recently found that global deletion of TRPC1 produces phenotypes similar to FHH [1]. These TRPC1 null mice have mildly elevated serum Ca in both fasted and unfasted conditions from 3.5 through 21.5 months of age, and inappropriately elevated parathyroid hormone (PTH) levels. They also have hypocalciuria, similar to FHH patients. While they have slightly elevated serum Mg and PO4, the differences are not significant [1]. The elevated PTH and borderline high serum PO4 are not secondary to renal failure, which develops only much later [2,3].

TRPC1 knockout mice are shown to have increased bone mass [1]. We now present data demonstrating that they have decreased urinary PO4 [4], decreased serum alkaline phosphatase (ALP) [5], decreased serum tartrate-resistant acid phosphatase (TRAP) [5], but elevated ALP/TRAP ratio [5], suggesting decreased bone turnover. Urine hyroxyproline was also found to be decreased [5], consistent with decreased collagen breakdown [6,7]. Although these chemical changes are not specific for bone metabolism, collectively, one unifying interpretation is increased bone accretion in global TRPC1 depletion, possibly mediated by the empirical increase in renal Ca and PO4 retention.

In vivo and *in vitro* experiments demonstrate that high extracellular fluid Ca does not appropriately suppress PTH in TRPC1 deletion. The downstream mechanism for this PTH insensitivity is explored recently [1]. The animal model studied is a global knockout, raising questions on the relative contributions by individual organs. Tissue culture studies demonstrate that PTH is influenced by the deletion of TRPC1 gene, excluding input from intestinal absorption, kidney reabsorption, and/or bone resorption [1]. The balance of Ca is physiologically regulated to ensure homeostasis and viability of the organism. The increased bone in null mice is only possible because of enhanced mineral balance, likely more Ca and more PO4 retention. Either the gut absorbs more Ca & PO4, and/or the kidney retains more Ca & PO4. Based on this assumption, at least in theory, hypocalciuria, a kidney defect in null mice, is expected to produce a bone phenotype. In brief, it is possible that the kidney and the bone effects are related. By the same token, the reduced renal PO4 clearance in null mice also contributes to the increased bone phenotype, again, a testable assumption. Conceivably input from any or all of these systems is likely. Indeed, if there were a kidney defect leading to increased renal reabsorption of Ca and PO4, this could result in increased deposition of Ca and PO4 in the bone. However, if TRPC1 decreases the secretion of FGF23 from osteoblasts [5,8], this would increase PO4 balance [8].

Mean serum P in unfasted animals was not statistically different in all 3 genotypes [1]. Renal P clearance is diminished in TRPC1 null mice at 8 months (48 vs. 67 ul /min in wild type mice) despite comparable food intake [4]. Hypocalciuria is seen in null mice [1]. FGF23 is down in null mice by 51% at 4 months and by 32% at 5 months [4]. Tartrate resistant acid phosphatase (TRAP) is lower in null mice, consistent with increased bone density. The ratio of serum ALP to serum TRAP is also increased in null mice, reinforcing the interpretation of increased bone density or decreased bone turnover [9]. Urine hydroxyproline is also decreased in TRPC1 null mice at 16 months [5], consistent with decreased collagen breakdown [6]. Bone was heavier at 7 months, corroborating previously published bone density data [1,5].

It is possible that the increased Ca and PO4 retention is responsible for the increased bone mass. However, the reduced carboxy terminal FGF23 could be due to a hitherto unknown effect of TRPC1 on the production and/or processing of FGF23 in the osteoblasts [10-13]. In addition, serum ALP & serum TRAP are both reduced, although the greater reduction in serum TRAP relative to serum ALP suggests less bone breakdown.

The increased bone weight by 25 % in the 7 month old TRPC null mice [5] corroborates the increased bone mass reported earlier [1].

Our recent paper suggests that TRPC1 functions downstream of CaSR to mediate parathyroid hormone secretion. Kidney-specific and bone-specific knockout mice would be expected to produce insights on the regulation of Ca and PO4 balance in whole animals. While mouse strains exist that could be used to generate bone cell-specific [14] and kidney-specific knockouts [15], studies in these organ-specific knockout mice could be lengthy and expensive. Classic studies utilizing parathyroidectomized mice [16,17] and/or micro punctured kidneys [17] would also elucidate mechanisms involved, but these experiments would be costly and time-consuming.

Acknowledgement

Research support by The Oklahoma Fraternal Order of Eagles.

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