Strontium as a Tracer for Calcium in Biological and Clinical Research

The calcium ion is required for the operation of a number of physiological processes, such as bone and tooth formation, blood coagulation, nerve impulse transmission, and muscle contraction. At the cellular-biochemical level, the calcium ion participates in signal transduction and is a significant factor in cell replication and cell division. The ultimate source of this important element is the diet, and the proper absorption of calcium is required to meet body needs. Abnormal or inadequate calcium absorption is a contributing factor in certain disease states, including osteoporosis, vitamin D-deficiency rickets, vitamin D-dependent rickets types I and II, and chronic renal failure, to name a few. The continued study of calcium absorption and calcium metabolism in animals and humans is essential for further elucidation of basic mechanisms, for understanding of disease processes, and for assessment of the efficacy of therapeutic strategies. Importantly, the use of tracer methodologies in studies of calcium metabolism has provided valuable information not otherwise attainable.

The radionuclides of calcium that have been widely used with considerable advantage as tracers in the study of calcium and bone metabolism are the beta-emitting $^{45}$Ca and the gamma-emitting $^{47}$Ca. However, the use of radioactive substances in basic and clinical research is dwindling because of the costs of radionuclides, the costs of disposal of radioactive wastes, and the justifiable reticence of giving potentially hazardous radionuclides to human subjects, particularly to the young and the pregnant. Stable isotopes of calcium are available that have been beneficially used in human and animal studies but here the disadvantages are the cost of the stable isotopes of calcium ($^{44}$Ca, $^{48}$Ca) and the more specialized equipment required for their analysis. For these and other reasons, researchers have turned to the use of strontium as a surrogate for calcium.

The strontium and the calcium ions, members of the alkaline earth series (Group IIB of the Periodic Table), have many properties in common, both having a valency of 2+, similar ionic radii, and the ability to form complexes and chelates of various solubilities and various binding strengths. The relative binding affinity of Ca$^{2+}$ and Sr$^{2+}$ differs among anionic compounds, some preferring Ca$^{2+}$ and others Sr$^{2+}$. The binding of Sr$^{2+}$ to alginates exceeds that of Ca$^{2+}$ by factors of 1.5 to 4.3, whereas calcium is preferred in other interactions, e.g., binding to G-actin, blocking negative charges on membranes, and binding to collagen [1]. In most biological systems, preference in general is given to Ca$^{2+}$ over Sr$^{2+}$, although a marine organism, an Acantharia, constructs its internal skeleton of strontium sulfate [2]. In higher vertebrates, the bony skeleton is mostly composed of the highly insoluble calcium phosphate complex, hydroxyapatite. Strontium present in bone is usually considered a contaminant, with no physiological function at the trace values present therein. However, the usefulness of strontium as a potential therapeutic agent for osteoporosis has experimental support. For example, in recent studies, low doses of strontium are reported to have beneficial effect on bone formation in osteoporotic patients and, in some studies, strontium has been given as a salt, designated S 12911 [3, 4].

The upswing in interest in strontium as a useful analog of calcium in clinical research was preceded by the development of a large body of information prompted by the formation of radionuclides of strontium as byproducts of nuclear fission and atomic bomb detonation. $^{89}$Sr and $^{90}$Sr are the prominent radionuclides of strontium that are formed, with $^{90}$Sr being one of the most hazardous because of its deposition in the skeleton, its long biological half-life (~10 years), and a decay half-life of ~30 years. A major purpose of the earlier investigations was to find procedures for decreasing the body burden of radiostrontium in the event of contamination of the environment and food supply [5]. Although the preferential movement of calcium over strontium between compartments in biological systems has long been known, a primary objective of many studies in the 1950s and 1960s was to quantify the relative movement and the retention of these alkaline earth cations, and to devise procedures to minimize the body burden of radiostrontium. Concepts were developed to formalize the relationships between Ca$^{2+}$ and Sr$^{2+}$ in their progress along the food chain to humans. The degree of discrimination was defined by the ratio of Sr/Ca in one compartment with respect to a precursor compartment. For example, experimental studies showed that the Sr/Ca ratio in milk was 0.1 with respect to the ultimate precursor, the diet, for which the Sr/Ca ratio was assigned the value of 1.0 [6]. This means that calcium is enriched 10-fold over strontium in the transfer from diet to milk—because of the preferential translocation of Ca over Sr in the processes of intestinal absorption, renal tubular reabsorption, and milk secretion. Calcium also moves more rapidly than Sr across the placenta from dam to fetus [7]. Little discrimination occurs in the transfer of Ca and Sr from blood to bone [6]. Quantitatively, the discrimination of calcium over strontium during the course of absorption varies among vertebrate species and ranges roughly from 2.4 to 5.0 [8]. Lengemann [8], in his review, noted that increases in dietary calcium decreased the fractional absorption of both elements proportionately, that the relative absorption of Ca$^{2+}$ and Sr$^{2+}$ tracers was not appreciably different in different segments of the small intestine (duodenum, jejunum, ileum) despite differences in the degree of fractional absorption, and that vitamin D similarly increased the absorption of Ca$^{2+}$ and Sr$^{2+}$ (i.e., there is no apparent vitamin D-dependent change in the preferential absorption of Ca$^{2+}$ over Sr$^{2+}$). Because of the high degree of absorption of calcium in infants, particularly from milk...
sources, little difference in the relative absorption of Ca and Sr is seen.

The mechanism of discrimination between Ca\(^{2+}\) and Sr\(^{2+}\) is certainly a consequence of interactions that occur during their transfer from one compartment or site to another. For intestinal absorption, the preferential absorption of Ca\(^{2+}\) over Sr\(^{2+}\) can be explained, at least in part, by current views of the way that calcium is absorbed from the ingesta. Two factors in the trancellular path of absorption that are involved in the uphill transport of calcium can be implicated as part of the discriminatory process, these being the high-affinity calcium-binding protein, calbindin, that presumably serves to increase the intracellular diffusion of calcium, and the plasma membrane ATP-dependent calcium-pump that actively extrudes calcium from the enterocyte [9]. Binding of Ca\(^{2+}\) to each of these proteins is considerably greater than that of Sr\(^{2+}\) [10, 11]. In addition to active transport, calcium also moves across the intestinal membrane by a paracellular, diffusional-type process, and that path also seems to give preference to the movement of Ca\(^{2+}\) over Sr\(^{2+}\).

Numerous studies have appeared more recently in which Sr was indeed used as an analog of Ca, only a few of which are referenced here because of space constraints. Many of these, such as those cited, have provided an assessment of the usefulness of Sr in clinically related investigations. For example, Blumshon et al. [12], as a result of their study, stated that stable strontium is a useful replacement of calcium in routine clinical assessment of the absorbability of dietary calcium. The preferential absorption of Ca\(^{2+}\) over Sr\(^{2+}\) they reported was \(1.9\), not too dissimilar to the value obtained by Spencer et al. [13] >30 years ago. Milsom et al. [14] likewise concluded that a Sr\(^{2+}\) absorption test is a useful procedure in the clinical assessment of Ca\(^{2+}\) absorption in human patients, and observed a preferential absorption of Ca\(^{2+}\) over Sr\(^{2+}\), also by a factor of \(1.9\). An increase in Sr\(^{2+}\) absorption in hyperparathyroid patients and a decrease in patients with celiac disease were shown by Milsom et al. [14], results expected from prior studies on calcium metabolism. High correlations (\(r = 0.9\)) between the absorbability of Ca and Sr in patients who were idiopathic hypercalciuric stone formers and in patients with osteoporosis, hypothyroidism, and growth-hormone deficiencies were reported by Sips et al. [15] and by Reid et al. [16] in patients with various disorders of calcium metabolism.

Vezzoli et al. [17], in this issue, effectively used stable strontium as a tracer of calcium absorption in their study of normocalciuric subjects with calcium kidney stones. The urinary excretion of absorbed Sr was also examined but found not to correlate with calcium excretion. This result is not too surprising in view of the sequence of events that occur between the glomerular filtration of Ca and Sr and their subsequent excretion in urine. Unlike intestinal absorption in the adult, most of the filtered Ca and nearly as much of the filtered Sr is reabsorbed. Therefore, small changes in the reabsorption processes as a result of imposed variables or disease states will result in large effects on the relative urinary excretion of these alkaline earth cations. Experimental studies in animals have shown, in fact, that the relative clearance of Ca and Sr can be extensively altered by various manipulations, such as feeding low-calcium diets or feeding diets of different Ca/P ratios [6]. Intravenous infusion of calcium decreased the efficiency of Ca reabsorption but decreased the efficiency of Sr reabsorption to a greater degree, thereby modifying the Sr/Ca ratio in the urine with respect to the Sr/Ca ratio in plasma.

Walser and Robinson [18] critically examined renal Sr/Ca relationships in dogs and humans and developed a mathematical means of relating the clearance of these cations to one other. Their approach was based on the physiologically reasonable premise that the rate of reabsorption of these alkaline earths from tubular fluid in the nephron is a direct function of their concentration in that fluid. The equation developed on the basis of the above premise and information is: \(\text{Sr}_{\text{u}}/\text{Sr}_{\text{r}} = (\text{Ca}_{\text{u}}/\text{Ca}_{\text{r}})^{0.7}\), where \(\text{Sr}_{\text{u}}\) and \(\text{Ca}_{\text{u}}\) = strontium and calcium excreted in urine, and \(\text{Sr}_{\text{r}}\) and \(\text{Ca}_{\text{r}}\) = strontium and calcium filtered, the latter requiring knowledge of the concentration of filterable cations in plasma and the glomerular filtration rate. The exponential value of 0.7 was found to be about the same for control dogs and those with metabolic acidosis, with metabolic alkalosis, or given thiazide diuretics. The same value, 0.7, pertained to normal human subjects and those with either Addison disease, hyperaldosteronism, or hyperparathyroidism. As the equation indicates, the rate of reabsorption of Sr is 0.7 of that of Ca. The standard error of estimate of this value over a wide range of variation was 15%.

Marcus and I used a similar treatment [19] to describe the comparative intestinal absorption of Ca and Sr as affected by the presence of lactose or lysine, compounds that substantially increase calcium absorption and consequently alter the ratio of absorbed Ca and Sr. Interestingly enough, analysis of the comparative absorption of Ca and Sr by the Walser–Robinson procedure gave an exponent that averaged −0.72, close to the value shown above for the renal excretion of these cations.

In summary, the data now available strongly support the view that Sr is a useful tracer for calcium in systems where a direct precursor–product relationship can be identified and sampled, such as intestinal absorption, placental transfer, and milk secretion. In contrast, the urinary excretion of tracer Sr does not directly reflect the urinary excretion of Ca because of the differential tubular reabsorption events that precede their appearance in urine. However, analysis of renal excretion data by the Walser–Robinson equation does provide a way of relating urinary excretion of Sr and Ca to their respective rates of tubular reabsorption. It seems apparent that strontium will continue to be used, and increasingly so, as a pseudo-calcium in clinical and physiological experimentation. Studies like that of Vezzoli et al. [17] will help define the advantages and disadvantages of strontium in this role.
References


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