SHORT COMMUNICATION

Hypocalcemia following strontium injection is associated with serum parathyroid hormone and calcitonin levels in rats

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Introduction

It is well known that whereas the rate of calcitonin (CT) secretion is a positive linear function of the calcium concentration in blood, there is an inverse relationship between parathyroid hormone (PTH) secretion and the serum calcium level¹⁾. Thus, an increase in the calcium level in blood enhances CT secretion, and reduces PTH secretion. Furthermore, strontium *in situ* has also been shown to enhance CT secretion²⁾ and suppress PTH secretion³⁾. These reports suggest that strontium has effects similar to those of calcium on the release of these hormones. However, previous reports have failed to explain two important points : 1) An increase in CT release has been observed in the absence of any change in the plasma calcium level²⁾, and 2) Since the blood sample for PTH determination is obtained directly from the parathyroid vein, the calcium level is not determined³⁾. Thus the relationship between calcium, strontium, and PTH and CT levels in blood *in vivo* is not yet clear, and a simultaneous determination of these divalent cations and hormones is necessary to evaluate the acute influence of strontium.

Materials and Methods

Seventy five female Wistar rats were used (body

weight of about 150 g). After a 24-hr fast, strontium (33.33 mmol/kg of SrCl₂ solution, n=69) (Sr group) or vehicle (0.3 ml of 0.15 M NaCl, n=6) was injected subcutaneously into the rats. Rats were sacrificed at 0.5, 1, 2, 4, 6, 8 and 24 hours after strontium injection. Blood samples were collected at each time point. Serum PTH and CT concentrations were measured at 0.5, 1, 2, and 4 hours after the injection. Serum calcium and strontium levels were also determined at each time point. Control rats which had been injected with the vehicle alone were sacrificed at 5 hours after the vehicle injection, and blood samples were collected. Serum calcium, CT and PTH were also measured in these rats. The treatment of the experimental animals was approved by the Experimental Animal Committee of Showa University.

Blood samples were obtained from the carotid artery under ether anesthesia, separated and stored at -20°C until use. Serum calcium and strontium were determined using an atomic absorption spectrophotometer (Model 473, Perkin Elmer Co., Ltd). CT and PTH in the serum were measured by radioimmunoassay systems (Calcitonin kit "Daiichi", Daiichi Radioisotope Labs, Ltd, and PTH-C "Eiken Chemical Labs, Ltd, respectively).

Results and Discussion

An acute increase in blood calcium results in a

Fig. 1 Time course of changes in serum calcium ($\circ$) and strontium ($\bullet$) concentrations following strontium injection (33.33 mmol/kg, as SrCl_2 , $n=6 \sim 11$ at each point). Rats in the control group were injected with vehicle alone (0.3 ml of 0.15 M NaCl, $n=6$). Values in the experimental group are expressed as the mean $\pm$ SEM. ** $p \leq 0.01$, compared to the control value.

proportional increase in serum calcitonin (CT)¹¹. In this study, both hypocalcemia and an increase in CT were observed following strontium injection (Figs. 1 and 2). These results clearly indicate that strontium may regulate CT release. A similar observation of CT release has been reported using strontium-perfusion technique in the pig²¹. Although the mechanism of strontium action in CT release is not clear, the increase in CT might reduce bone resorption, *via* osteoclasts, which would reduce the calcium level in blood⁹. Furthermore, CT increases the urinary excretion of calcium⁹. Thus, hypocalcemia may have resulted primarily from the increase in CT release.

There have been some studies of the effect of strontium on parathyroid hormone (PTH) secretion. Strontium clearly enhances the intracellular accumulation of inositol phosphates and inhibits cAMP accumula-

Fig. 2 Time course of changes in serum parathyroid hormone (PTH, $\circ$) and calcitonin (CT, $\bullet$) following strontium injection (33.33 mmol/kg, as SrCl_2 , $n=6$ at each point). Rats in the control group were injected with vehicle alone (0.3 ml of 0.15 M NaCl). Values are expressed as a percentage of the control (mean $\pm$ SEM). *, $p \leq 0.05$, **, $p \leq 0.01$, compared to the control value.

tion in bovine parathyroid cells in a dose-dependent manner⁶, and perfusion of the parathyroid gland with strontium has been shown to cause a pronounced decline in the rate of PTH secretion³. In this study, the serum PTH level decreased significantly, but not drastically (Fig. 2). Although it is not clear whether the decrease in PTH release produces a hypocalcemic response, it clearly does not induce an increase in the serum calcium level.

It is well known that strontium-feeding induces a reduction in intestinal calcium absorption by decreasing the serum $1\alpha, 25\text{-dihydroxyvitamin D}$ ($1,25(\text{OH})_2\text{D}$) level^{7,8}. The serum $1,25(\text{OH})_2\text{D}$ level was not determined in this study. Thus, the effects of strontium on vitamin D metabolism have still not been determined in an acute study. In this study, the effect of strontium, *via* $1,25(\text{OH})_2\text{D}$, on intestinal calcium absorption might be ruled out by fasting.

Strontium has been shown to directly suppress osteoclast activity⁹. Solh and Rousselet¹⁰ reported

that the injection of strontium induced hypercalciuria. Thus, hypocalcemia may have, in part, resulted from a reduction in osteoclast activity and/or hypercalciuria induced by strontium itself.

In conclusion, a toxic dose strontium may induce hypocalcemia as a consequence of, at least in part, an increase in CT release and a decrease in PTH release *in vivo*.

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