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Role of pituitary hormones in regulating renal vitamin D metabolism in man

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Summary and conclusions

Studies in animals and tissue culture have shown the importance of prolactin and growth hormone in regulating renal 1α-hydroxylase activity and plasma concentrations of 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D$_3$). Evidence for a similar role for these hormones in man was sought by using a radioreceptor assay to measure plasma 1,25(OH)$_2$D$_3$ concentrations in 20 normal subjects, 12 patients receiving dialysis, 11 patients with primary hyperparathyroidism, 10 pregnant women, seven women with prolactinoma, and 14 patients with acromegaly. Circulating 1,25(OH)$_2$D$_3$ concentrations were appreciably raised in the patients with primary hyperparathyroidism and the pregnant women ($P < 0.001$), slightly but significantly increased in the patients with prolactinoma ($P < 0.05$), and greatly raised in those with acromegaly ($P < 0.001$).

These results suggest that prolactin and growth hormone are important regulators of renal vitamin D metabolism in the physiological conditions of pregnancy, lactation, and growth in man.

Introduction

Renal regulation of vitamin D metabolism has been controversial, but the concept of parathyroid hormone as the only important regulatory factor is now clearly completely untenable.[1] Considerable evidence indicates that the increased calcium demands made during physiological conditions of calcium stress, such as pregnancy, lactation, and growth, are met by increased production of 1,25-dihydroxycholecalciferol (1,25(OH)$_2$D$_3$).[2] The recent findings that prolactin[3] and growth hormone[4] stimulate the production of 1,25(OH)$_2$D$_3$ in experimental animals indicate that these pituitary hormones may be important regulators of renal vitamin D metabolism in natural (as opposed to experimental) calcium stresses. We present here the results of studies of circulating 1,25(OH)$_2$D$_3$ concentrations, which strongly suggest that these hormones fulfil the same role in man as in experimental animals.

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Subjects and methods

We studied the following groups of subjects: 20 normal subjects (11 men, nine women) aged 19-48 (mean 29·4); 12 patients receiving dialysis (nine men, three women) aged 21-25 (mean 23·8); 10 healthy women at 33-34 weeks of pregnancy, aged 23-39 (mean 26·9); 11 patients with primary hyperparathyroidism (three men, eight women) aged 29-72 (mean 49·8); 14 patients with acromegaly (seven men, seven women) aged 36-61 (mean 49·9); and seven women with prolactinomas, aged 18-47 (mean 29·3). Seven of the 14 patients with acromegaly had received treatment, but all had raised concentrations of growth hormone at the time of the study. Two of the women with acromegaly were postmenopausal as shown by stimulation with luteinising hormone-releasing hormone, but the other women with acromegaly or prolactinoma had normal gonadotrophin response. Stimulation with thyrotrophin-releasing hormone was performed in 10 of the patients with acromegaly and all those with prolactinoma. All patients were euthyroid, although the response of thyroid-stimulating hormone was depressed in the seven who had received treatment for acromegaly. All patients were taking their normal diet. None were taking vitamin D preparations or had evidence of vitamin D deficiency.

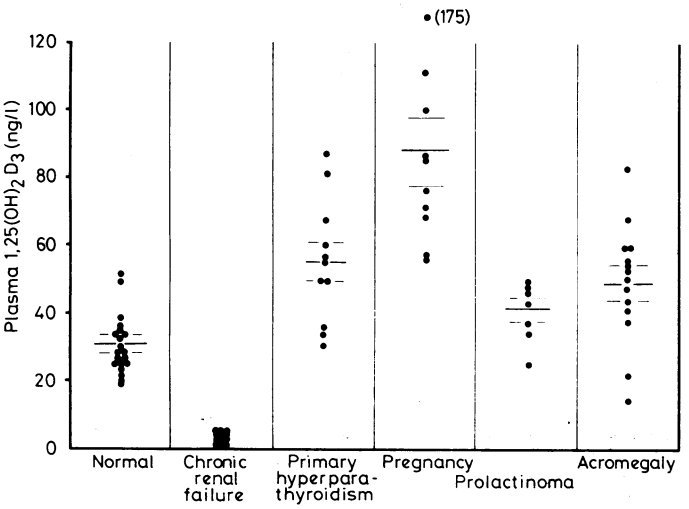
Morning samples of plasma were stored at −20°C until assay. Our assay for plasma 1,25(OH)$_2$D$_3$ concentrations was developed from that of Brumbaugh *et al*[5] but entailed using an intestinal receptor preparation and Sephadex column chromatography[6] and high-pressure liquid chromatography modified from the method of Matthews *et al.*[7] The precision of the method is ±4 pg/ml.

The results in each group were compared with normal values by means of a two-sample *t* test.

Results

The figure shows the results in the different groups of subjects. The mean ± SE of mean plasma 1,25(OH)$_2$D$_3$ concentration in normal subjects was 29·4±1·9 ng/l; in patients with chronic renal failure receiving dialysis < 10 ng/l; in patients with primary hyperparathyroidism 55·0±5·5 ng/l ($P < 0.001$); in pregnant women 87·7±11·2 ng/l ($P < 0.001$); in patients with prolactinomas 40·4±3·25 ng/l ($P < 0.05$); and in patients with acromegaly 47·7±4·6 ng/l ($P < 0.001$).

Thus the 1,25(OH)$_2$D$_3$ concentration was altered in primary hyperparathyroidism, prolactinoma, and acromegaly and in pregnancy. The ranges in normal subjects and patients with chronic renal failure were similar to those reported.



Plasma $1,25(OH)_2D_3$ concentrations in all subjects studied. Bars indicate mean ± SE of mean values.

Discussion

Raised $1,25(OH)_2D_3$ concentrations have been reported in primary hyperparathyroidism, but, interestingly, we found some values to be within the normal range (figure). This fits well with the idea that parathyroid hormone has two effects: to stimulate production of the active metabolite by the kidney; and to increase plasma calcium concentrations by an independent action to enhance renal tubular calcium resorption. Clearly sometimes the increased calcium concentration will exert a powerful depressing effect on $1,25(OH)_2D_3$ synthesis outweighing the direct stimulatory effect of parathyroid hormone. This agrees closely with earlier experimental findings and concepts.[8]

The most striking changes seen were in pregnancy, when all values were above the normal range. These results agree well with those of other workers[2 9] and provide a satisfactory explanation for the increased calcium absorption that occurs in pregnant animals and women. The factors responsible for the increased concentrations of $1,25(OH)_2D_3$, however, are not yet known, although parathyroid hormone, oestrogen, prolactin, and placental lactogen, which are all raised at some stage of pregnancy, are known or proposed regulators of renal vitamin D metabolism.

Plasma concentrations of parathyroid hormone start to rise after the 36th week of pregnancy,[10] but our results show extremely high plasma $1,25(OH)_2D_3$ concentrations before this. In contrast, plasma concentrations of oestrogen, prolactin, and placental lactogen are raised during early human pregnancy. Oestrogens are potent stimulators of renal 25-hydroxy vitamin D_3 1α-hydroxylase (25-OHD_3-1α-hydroxylase) in birds,[11] although studies in man have shown that exogenous administration of oestrogen does not increase calcium absorption.[12] Prolactin also stimulates production of $1,25(OH)_2D_3$ in birds,[3] and studies with bromocriptine in lactating rats[13] suggest that it may have a similar effect in mammals in the proper physiological setting. Similarly, placental lactogen stimulates 25-OHD_3-1α-hydroxylase activity in birds (E Spanos, unpublished work) and enhances calcium absorption in mammals.[14] Thus the pituitary and placental hormones, rather than the parathyroid hormone, are the probable regulators in pregnancy.

Interestingly, the plasma concentrations in patients with prolactinoma were only slightly, though significantly ($P < 0.05$), increased. There is no correlation between plasma concentrations of $1,25(OH)_2D_3$ and prolactin. Clearly the effects of prolactin shown only in lactation in animals are not important in prolactinoma, though are likely to be relevant during pregnancy.

The significantly increased ($P < 0.001$) circulating $1,25(OH)_2D_3$ concentrations in patients with acromegaly explain the altered calcium metabolism in this condition and strongly suggest that growth hormone stimulates production of $1,25(OH)_2D_3$ in man as it does in the rat.[4] The wide range of values and the lack of correlation between plasma concentrations of $1,25(OH)_2D_3$ and growth hormone, however, indicate that other factors, perhaps including the stage of the disease, are important.

Thus the main physiological role of $1,25(OH)_2D_3$ appears to be enhancing absorption when extra calcium and phosphorus are needed. This is mainly during growth, pregnancy, and lactation, and $1,25(OH)_2D_3$ may perhaps best be regarded as a hormone whose most vital role is to provide the calcium and phosphorus requirements of the fetus and growing child. These concepts were developed from earlier work in experimental animals,[3 4] but our studies show that they are probably also valid in man. The pituitary hormones are probably very important in these conditions, although placental lactogen and oestrogen may also play a part during pregnancy and parathyroid hormone in lactation. In any event, early disagreements about regulation seem resolved with the recognition of the multifactorial nature of the control of vitamin D metabolism.

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ONE HUNDRED YEARS AGO A petition is being signed in Edinburgh to two ladies, asking them to allow themselves to be nominated as managers of the Royal Infirmary, Edinburgh, at the approaching election in January, by the Court of contributors. The petition states that, as nearly one-half of the patients are female and the nursing-staff entirely so, the petitioners think it right there should be some female managers. (*British Medical Journal*, 1880.)