THE REGULATION OF VITAMIN D METABOLISM IN THE KIDNEY AND BONE

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Abstract

The activation of 1,25D-dihydroxyvitamin D_3 (1,25D) is catalysed by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) in the kidney, which is the primary producer of 1,25D in the body. Although the synthesis of 1,25D by CYP27B1 and the catabolism of 1,25D by 25-hydroxyvitamin D-24-hydroxylase (CYP24) also take place in the bone, the significance of the bone cell-specific metabolism of vitamin D remains largely unknown. This thesis investigates the regulation of the expression of CYP27B1, CYP24 and vitamin D receptor (VDR) mRNA, both in the bone and in the kidney, with the aim to determine whether the regulation of the vitamin D metabolism in the bone is independent from that in the kidney. The effects of age, dietary calcium and vitamin D status on the expression these genes in both the kidney and the bone, as well as on a number of biochemical factors known to regulate the renal metabolism of 1,25D, such as PTH, calcium and 1,25D itself, were examined. CYP27B1 mRNA expression was also studied in histological sections of rat femoral bone. Furthermore, CYP27B1, CYP24 and VDR mRNA expression were also identified in specific regions of the rat femur and in a number of bone cell lines, with the aim to identify the bone cell types that have the capacity to metabolise and/or to respond to vitamin D.

The age-related decrease in the circulating levels of 1,25D detected in animals ranging in age from 3 weeks to 2 years old, was a direct result of a reduction in the expression of CYP27B1 mRNA and an increase in the expression of CYP24 and VDR mRNA in the kidney. In contrast, the expression of CYP27B1 and CYP24 mRNA in the bone is high from 3 to 15 weeks of age, which is the period of rapid growth and development. The expression of CYP27B1 mRNA in the bone was positively correlated with the circulating levels of calcium throughout aging, which suggests that the 1,25D

produced in the bone may be involved in the mineralisation process. The positive correlation found between the expression of CYP27B1 and CYP24 mRNA in the bone was in contrast with the negative correlation found between the expression of these two enzymes in the kidney. This suggests that the 1,25D produced locally in the bone, rather than the 1,25D produced in the kidney, is the primary determinant of the CYP24 activity in the bone.

In vitamin D-deplete animals, fed a 0.1% calcium diet (D(-)/LC), the expression of CYP27B1 mRNA was induced and the expression of CYP24 mRNA was suppressed in the kidney. In contrast, both the expression of CYP27B1 and CYP24 mRNA were low in the bones of these D(-)/LC animals. When vitamin D-deplete animals were fed a 1% calcium diet (D(-)/HC), the expression of both CYP27B1 and CYP24 mRNA was high in the bone, which was in direct contrast with the low expression of these genes detected in the kidney. Besides this, a positive correlation was found between the expression of CYP27B1 mRNA in the bone, serum calcium levels and bone mineral volume (BV/TV) in the epiphysis, which supports the findings for the age study that the locally produced 1,25D may be involved in the promotion of bone mineralisation. Although serum PTH levels was positively correlated with the expression of CYP27B1 mRNA in the kidneys of hypocalcaemic animals, there was no such relationship detected between the levels of serum PTH and the expression of CYP27B1 mRNA in the bone. This finding suggests that the regulation of the expression of CYP27B1 mRNA in the bone is different from the regulation found in the kidney. The identification of CYP27B1 mRNA in osteoblasts-like cells, taken together with the associations between serum calcium and CYP27B1 mRNA expression in the previous studies, suggests that 1,25D produced in osteoblasts may

play a significant role in the bone mineralisation process. The detection of CYP27B1 mRNA expression in a number of bone marrow cells suggests that locally produced 1,25D may also play a role in the growth and differentiation of hematopoietic cells.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I give my consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

Signature …….

Date ……./……./…….

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Publications Arising

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Anderson PH, Iida S, Moore A, Cochran M, O'Loughlin P, May B and Morris H. 2001 Bone CYP27B1 mRNA is regulated by dietary calcium and not vitamin D. Journal of Bone and Mineral Research 16 (1): 313s

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Presentations Arising

International

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Awards Arising

Young Investigator Award Finalist. 2000 National Australian & New Zealand Bone and Mineral Society Conference. Hamilton Island, Queensland.

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