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Voyages of Discovery

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Abstract

The metabolism of calcium and bone is controlled by five principal hormones: parathyroid hormone, 1,25-dihydroxyvitamin D, calcitonin, parathyroid hormone-related peptide and fibroblast growth factor 23, some of which have been known for several decades and some of which have only recently been identified. The stories of discovery of these hormones have constituted a series of complex journeys which have been undertaken over the past century or so and none of which has yet been completed. The complexities of bone and calcium metabolism have been and remain, to many people, somewhat mysterious and a daunting task to understand. This book is designed to try to unravel those mysteries and present them in an interesting and comprehensible manner.

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The study of the diseases that affect bone and calcium has made huge strides over the past few decades. The initial realisation that rickets, which was rife in industrial cities, particularly in the UK, could be cured by exposing children to sunlight or supplementing them with foods such as cod liver oil was a major step in improving the health of children in the early part of the twentieth century. Subsequently, the discovery of other hormones that are involved in mineral metabolism, both calcium and phosphate, has enabled much wider understanding of the mechanisms of disease to be gained. This has led to the introduction of logical treatments based on this scientific understanding.

There are five major hormones, vitamin D and its metabolites, parathyroid hormone (PTH), calcitonin (CT), parathyroid hormone-related peptide (PTHrP) and fibroblast growth factor 23 (FGF23), that are involved directly in the control of mineral metabolism in man. In addition, several other hormones, such as oestrogens and androgens, cortisol, growth hormone and thyroxine, have modifying effects. The story of the unravelling of these hormones is a long and complicated one that has gradually revealed itself over the past century or so. For each there has been a long voyage of discovery, some lasting longer than others, but each is still a journey in progress.

Vitamin D and Rickets

Rickets is an ancient disease. It was probably known in the ancient world, but is recorded in the UK since the 17th Century [1]. It became widespread with the increase in industrialisation during the 19th and 20th centuries. The first breakthrough in treatment came with the realisation, shortly after the end of the First World War, that most rickets could be cured either by exposure to sunlight or with supplements of cod liver oil [2]. Vitamin D was discovered to be the agent that effected the cure. As a consequence of this, rickets virtually disappeared in the UK until the first major wave of immigration, mainly from the old commonwealth countries. Most of this immigration was from either south Asia or the Caribbean and brought with it a greater predisposition to rickets than was present within the white population because of the need for greater sunlight exposure of more darkly pigmented skin in order to synthesise sufficient vitamin D [3]. This resulted in a second wave of rickets that again occurred mainly in the industrialised cities. Following a pilot study, it was demonstrated that the incidence of rickets in Glasgow could be effectively reduced by a campaign of supplementation [4]. Since then, the incentives to persist in such a campaign appear to have been lost and a third wave resurgence of rickets has been seen in many countries of the world [5].

In the meantime, during the 1960s it was discovered that vitamin D required metabolism in order to become effective and elevated it from the status of 'vitamin' to one of 'hormone'. As a consequence, some forms of rickets that had previously been thought to be caused by vitamin D deficiency were now understood to result from inborn errors of metabolism and explained why some children had not previously responded to vitamin D treatment. Since then the metabolism of vitamin D has been well worked out and provides a logical basis for treatment.

The third stage of investigation of vitamin D has been the demonstration that vitamin D deficiency may play an important part in contributing to the aetiology of a number of common diseases that previously had not been associated with vitamin D deficiency. These include certain cancers, especially of the breast and colon, diabetes, both type 1 and type 2, and coronary heart disease. These relationships remain to be worked out although increasing evidence is accumulating that vitamin D plays a part in the prevention of many of these diseases [6]. Whilst they are generally diseases of adulthood, it is conceivable that their origins lie in childhood.

Vitamin D remains the preferred treatment of vitamin D deficiency but it seems extraordinary that, in modern societies, the ability to eliminate a fully preventable disease eludes us. It is arguable that effective vitamin D supplementation is the single most cost-effective treatment that could be given, at least to 'at risk' populations.

Parathyroid Hormone

During the 1920s the role of the parathyroid glands in secreting a calcium-raising hormone was clarified [7]. The first description of hypoparathyroidism was made in 1929 [8] and this was followed in 1942 by the description of parathyroid hormone resistance in pseudohypoparathyroidism [9]. Fuller Albright was an early pioneer of parathyroid physiology and pathology who laid the basis of much of what we know about basic parathyroid actions. He was correct in describing pseudohypoparathyroidism as a hormone resistance syndrome. However, as it turns out, he was incorrect in referring to it as 'an example of Seabright bantam syndrome'. The 'Seabright bantam', named after Sir John Sebright (sic), was misspelt in the original paper. It is characterised by the cock birds having a 'hen-feathering' appearance which led to the misapprehension that they were resistant to testosterone. In fact, they have excessive activity of aromatase P450 in extragonadal tissues that converts testosterone to oestrogen [10]. It is this that causes the characteristic feathering pattern. In most other aspects, he was correct and he made a huge contribution to our understanding of bone disease and several conditions bear his name eponymously.

The first immunoassays for PTH were described in 1969 [11]. These had been developed in the wake of other immunoassays such as those for insulin and growth hormone. However, it rapidly became apparent that these were not straightforward since PTH, a large molecule containing 84 amino acids, circulates as a number of fragments [12]. These are particularly problematic in the presence of renal failure when the inactive fragments tend to circulate in higher quantities than normal. Since the original assays were developed, further refinements have been made that now allow measurement of physiological levels of intact hormone.

The structure of PTH was difficult to establish and different structures were proposed initially. Once these were resolved, it became apparent that, although PTH contains 84 amino acids, only the first 34 are required for full biological activity [13]. The function of the remainder of the molecule remains unclear. Subsequent work revealed the mechanism of action of PTH via the Gsα second messenger which is common to a number of polypeptide hormones and which provides an explanation for the hormone resistance state known as pseudohypoparathyroidism that was originally described by Fuller Albright.

Calcitonin

This hormone was first described in 1963 [14] and its structure elucidated in 1968 [15]. It is a 32 amino acid protein and, unlike PTH, has a disulphide bond between the cystine residues at positions one and seven. It has an action that is largely opposite to that of parathyroid hormone, i.e. it has a calcium-lowering effect. There are considerable interspecies differences in structure [16] and, interestingly, the salmon

hormone has considerably greater activity than its human counterpart in humans. For this reason, it has been used as a therapeutic agent to lower calcium in certain hypercalcaemic conditions although its use in this respect has been largely superseded by the introduction of the bisphosphonates.

CT is now known to be one product of the α-CT/CT gene-related peptide (CALCA) which, as a result of alternative splicing, gives rise to at least two products, α-CT and CT gene-related peptide (CGRP) [17]. Each is produced mainly by different tissues, CT by the C cells of the thyroid and CGRP by the hypothalamus. The physiological role of these proteins, together with those of two other closely related proteins, amylin and adrenomedullin, have yet to be identified precisely, but CT probably makes a contribution to bone formation and CGRP is mainly a neuropeptide which plays a part in vascular tone. It may have a role in the pathogenesis of migraine. Nevertheless, it is also thought that all four proteins may play some part in bone formation [18, 19] possibly via a network of neurones that exists in bone. However, pathological states in man in which CT is produced in excess, such as medullary carcinoma of the thyroid (MCT), do not result in hypocalcaemia and the principal significance of CT is as a marker of MCT and as a therapeutic agent.

Parathyroid Hormone-Related Peptide

The first indication that there is a substance that has PTH-like activity but is not PTH came with a publication in 1985 demonstrating that human umbilical cord blood contained a compound which had PTH-like bioactivity and yet could not be identified as PTH on immunoassay [20]. The calcium concentration in foetal cord blood is unusual in being one of the few substances which is present at higher levels than in the mother, i.e. there is a positive gradient across the placenta. Whilst it had previously been suggested that foetal PTH levels are suppressed because of these relatively high levels of calcium, the question had never been asked as to what maintains the gradient. It seems that it is PTHrP that is responsible.

Subsequently, a humoral factor was identified and purified from malignant tissue that was found to be responsible for some instances of humoral hypercalcaemia of malignancy [21]. This was a PTH-like factor that shared some properties with PTH, including its ability to stimulate cyclic-AMP, but was sufficiently dissimilar as to be undetectable on standard PTH immunoassays. It is a considerably larger molecule than PTH itself and has some limited homology with PTH such that it binds to the PTH1 receptor.

The role of PTHrP in man seems to be principally in the foetus to maintain the calcium gradient across the placenta and to have a paracrine function in promoting cartilage development. In postnatal life, it seems not to have a classical endocrine role but is important as a mediator of humoral hypercalcaemia of malignancy [22].

Fibroblast Growth Factor 23

The factors controlling phosphate metabolism have, until relatively recently, not been well understood. The discovery of FGF23 in 2000 [23] led to an explosion of discoveries relating to phosphate. The relationship of this to PHEX, DMP1, GALNT3, FGFR1, Klotho and the sodium/phosphate co-transporter in renal tubular cells has widened our understanding considerably and led to a much greater knowledge of the pathological processes that go towards explaining the mechanisms of disorders of phosphate metabolism. Further details of all these hormones are given in the relevant chapters.

The discovery of DNA in the early 1950s and its role as a genetic blueprint has allowed the identification of a whole host of diseases that are genetically based. The diseases related to bone and calcium are no exception and, if one excludes vitamin D deficiency and secondary osteoporosis, it is the case that virtually all other causes of bone and calcium diseases have a genetic origin. Indeed, they encompass the full gamut of genetic conditions including autosomal and X-linked dominant and recessive, mitochondrial and imprinting disorders. It is therefore necessary to have at least a modicum of understanding of genetics in order to be able fully to understand their mechanisms. Fortunately, modern technology allows the rapid advances in genetics to be recorded electronically without having to 'go back to the books' all the time. It also ensures that updates to discoveries can be made available to a wide audience more rapidly than previously. The most useful tool is the creation of the Online Mendelian Inheritance in Man (OMIM) website which was the brainchild of the late Victor McKusick [24] when his original paper version became too unwieldy and difficult to update. The website is accessible at http://www.ncbi.nlm.nih.gov/sites/entrez?db = omim and gives details of all disorders that are or are thought to be genetically based, together with the genes involved. Because of the diversity of the disorders of bone and calcium metabolism, each of the clinical chapters in this book is accompanied by at least one table that gives the OMIM reference numbers for these disorders and their genes. Each entry is accompanied by a detailed bibliography which is regularly updated. Hopefully, this will prove useful to readers.

An explanation of any abbreviations appearing in the text and which are not defined at the time can be found in the Appendix together with relevant conversion factors for readers who are not familiar with either SI or 'conventional' units of measurement.

The final chapter in this book is a series of case histories. These are intended to illustrate some of the problems that are discussed in the previous chapters. It is not a comprehensive coverage of all the conditions mentioned but, since this book will be available on line, it will be possible in the future to add further cases. When the text describes a case that is included in the case history section, the number of that case is shown in the text. References to these cases may appear in more than one chapter.

‘Dr. Donne’s verses are like the peace of God; they pass all understanding’. With these words, King James I of England and VI of Scotland is said to have replied to Archdeacon Plume when asked to comment on the poetry of John Donne [25]. There are many, even in the world of paediatric endocrinology, for whom the same is true of the study of bone and calcium disorders in children and for whom they remain a mystery. This was recognised by the late Graham Chapman, of Monty Python fame, comedian, bon viveur and erstwhile medical student, who, in a book of collected sketches, letters and essays, wrote a brief essay entitled ‘Calcium Made Interesting’ [26]. This book is designed not only to enable mineral metabolism to be understood, but to ‘make calcium interesting’.

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