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Landmark Discoveries in Calcium Metabolism Review of Literature

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Introduction

Calcium metabolism plays an integral role in maintaining homeostasis. Over 99% of the calcium present normally in the adult human body resides in the skeleton, where it provides mechanical stability and serves as a reservoir sometimes needed to maintain extracellular fluid (ECF) calcium concentration. Ionized calcium in the ECF must be maintained within a narrow range because of the critical role calcium plays in a wide array of cellular functions, especially in the neuromuscular activity, secretion, and signal transduction. Intracellular cytosolic free calcium levels are ~100nmol/L and are 10,000-fold lower than ionized calcium concentrations in the blood and ECF (1.1-1.3mmol/L). Cytosolic calcium does not play the structural role played by extracellular calcium; instead, it serves a signaling function. The steep chemical gradient of calcium from outside to inside the cell promotes rapid calcium influx through various membrane calcium channels that can be activated by hormones, metabolites, or neurotransmitters, swiftly changing cellular function. In blood, total calcium concentrations normally 2.2-2.6mM (8.5-10.5mg/dL), of which ~50% is ionized [1].

Calcium metabolism derangements are linked with a wide variety of diseases the most commonly known of which are rickets, osteomalacia, osteoporosis, hyperparathyroidism, hypoparathyroidism, Paget's disease of bone, renal osteodystrophy, osteogenesis imperfect, osteitisfibrosacystica, osteopetrosis and fibrous dysplasia. This review of literature focuses on some of the innumerable discoveries which have helped the understanding of calcium metabolism and have benefitted patients over the years.

Calcium

Calcium was first isolated by Sir Humphry Davy in 1808. Davy isolated calcium by electrolysis, putting a mixture of calcium oxide with mercury (II) oxide on a platinum plate (anode) with a platinum wire partially submerged into mercury as the cathode. Calcium was isolated from the calcium-mercury amalgam thus produced by distilling off the mercury [2].

But it was not until 1883 that the biological role of calcium was identified. Sir Sydney Ringer's four papers published in The Journal of Physiology in the early 1880s (1882a,b, 1883a,b) are rightly acknowledged as the starting point for the development of the modern understanding of the role of calcium in the contraction of the heart [3-8]. After this landmark discovery, many other physiological roles of calcium were identified by various researches like Ringer and Sainsbury who in 1894 described its role the development of the skeleton [4,9]. Campbell in 1988 demonstrated the role of calcium in conduction of nerve impulse to muscle [4,10], in 1988 Mooren & Kinne [11] described the importance of calcium in cellular functions necessary for both normal and diseased states of the cell [4,11], Heilbrunn and Wiercinski demonstrated that it was only calcium that could cause the muscle fiber to contract [4]. These and many other discoveries continued throughout the 19th and 20th century, but it was Dr. Fuller Albright who described the metabolism of calcium in detail in his book "Parathyroid Glands and Metabolic Bone Disease". He is credited with the discovery of calcium metabolism [12].

Parathyroid Glands and Hormone

The essential role parathyroid glands play to maintain life and its effect in pathophysiology is widely known today. This knowledge has the contribution of many inquisitive and great minds, few of which we are mentioning. It was Sir Richard Owen an English biologist, comparative anatomist and palaeontologist who first described the parathyroid glands – he found them in Indian rhinoceros in 1852 [13,14]. But the credit for the discovery of the parathyroid glands is generally accorded to Dr.Ivar Victor Sandstrom (1852-89), who, in 1880, when praelector in anatomy in the University of Uppsala, published the first systematic account

of these then 'new glands' [15].

Although Adolph M. Hansen extracted parathyroid hormone in 1923 from his work on cattle, [16] the honour for the discovery of this hormone is given to Canadian James Bertram Collip who extracted it, named it parathyrin and used it to treat tetany in the year 1925 [17]. Parathormone was isolated and purified by Rasmussen and Craig in 1959 who also gave its polypeptide structure in the year 1962 [18,19].

The understanding of parathyroid gland functioning came gradually over the years. Greenwald identified its phosphaturic action in 1911 [20], followed by the discovery of its resorptive effect on the skeleton by Barnicot in 1948 [21]. The same year, Jahan and Pitts described its anti-calciuric action [22]. Its effect on small intestine was discovered much later by RV Talmage & JR Elliott [23].

Vitamin D

Another important component of calcium metabolism is Vitamin D. It became the first vitamin to have a Nobel prize in its history when Adolf Windaus was given the Nobel prize for Chemistry in 1928 for his work on vitamins and sterols [24]. One of the first significant steps in the discovery of vitamin D was taken by Sir Edward Mellanby [25] who linked rickets with a fat soluble dietary nutrient. He wrote: "Rickets is a deficiency disease which develops in consequence of the absence of some accessory food factor or factors. It therefore seems probable that the cause of rickets is a diminished intake of an anti-rachitic factor, which is either [McCollum's] fat-soluble factor A, or has a similar distribution to it" [25]. Then in 1922, Elmer McCollum [26] and his colleagues identified an anti-rachitic factor that was not destroyed by oxidation and played an important role in bone formation. They named this factor Vitamin D [26].

Three teams of scientists – Hume & Smith [27], Goldblatt & Soames [28] and Steenbock & Black [29], confirmed that sunlight (UV light) is a source of vitamin D in 1924 by their experiments on rats [27-29]. Hess & Weinstock [30] simultaneously reported that UV irradiation of food not having anti-rachitic factor induced its production in these food items and could be used as a method to enrich food to improve public health [30].

Calciferol (Vitamin D-2) was purified and crystallized in the year 1931 by Reerink et al. [31] in London as well as by Windaus and his co-workers in the Netherlands [32]. The correct structure was described by Windaus and Thiele in 1936 [33, 34]. Then in 1936, Windaus et al synthesized cholecalciferol and named it Vitamin D3 [35]. While Velluz et al in 1955 gave the entire photochemical and thermal reactions involved in the production of cholecalciferol from ergosterol, [36] it was Holick et al. in 1980 who described the photoproduction of vitamin D in skin in its entirety [37] (Figure 1).

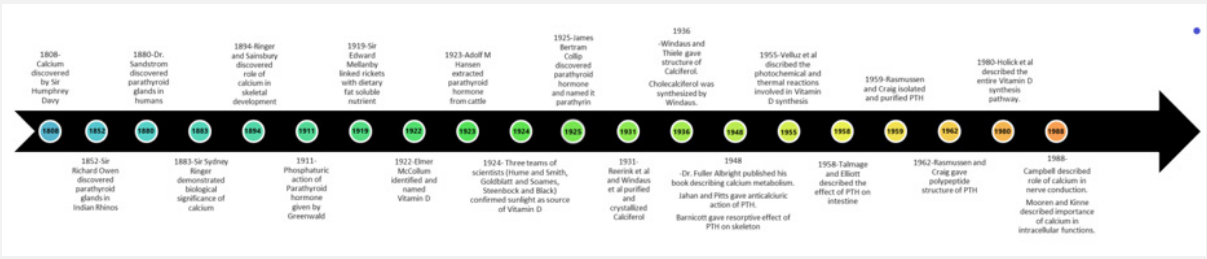

Figure 1: Photochemical and thermal reactions involved in the production of cholecalciferol from ergo sterol.

Calcitonin

Calcitonin was discovered in the year 1961 by Copp and purified in the same year by him and Cheney. Coppstated that, "While studying the control of its secretion in 1961, we discovered a second calcium-regulating hormone (calcitonin) which was released by hypercalcemia and lowered plasma calcium by inhibiting osteolysis. It is a straight-chain peptide with 32 amino acids and a 7-membered disulfide ring at the N terminal. It is produced by C cells which arise from the neural crest and is considered a neuropeptide hormone" [38].

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