Research Journal of Biological Sciences 6 (4): 183-186, 2011
ISSN: 1815-8846

Parathyroid Hormone and Calcitonin Regulating Calcium Levels

Stephanie Galea and Renald Blundell
Department of Physiology and Biochemistry, University of Malta, Msida, Malta

Abstract: Maintaining normal calcium levels within the body (8.5-10 mg dL^{-1}) requires the action of two hormones in particular: Parathyroid Hormone (PTH) and calcitonin (http://www.bloodbook.com/ranges.html). In lower calcium levels, PTH is released and works in such a way as to increase the calcium back to the normal range. Calcitonin acts exactly in the inverse way by targeting osteoclasts and osteoblasts. A somewhat constant amount of calcium is lost from the body through fecal excretion. In the gut, absorption and secretion of calcium and phosphate occurs, depending on the free ionized calcium in the extracellular fluid. The amount of calcium in the extracellular fluid also influences excretion of calcium in the renal system. The largest pool of calcium is found in bone which is essential in calcium homeostasis. This is because through bone remodelling, calcium may be taken up from the extracellular fluid or given up to the extracellular fluid depending on the presence of hormones in a process known as osteolytic osteolysis. The processes mentioned before are mediated through PTH, calcitonin and 1,25-dihydroxycholecalciferol.

Key words: Calcium, parathyroid hormone, calcitonin, bone, vitamin D and phosphate, Malta

INTRODUCTION

Calcium has several important functions in the body including enzymatic regulation (e.g., calmodulin), neuromuscular function, blood coagulation and hormone secretion. The free ionized calcium levels making up 48% of calcium in the blood, fluctuates and hormones act on this form on calcium to restore homeostasis. About 99% of calcium in the body is found in the form of hydroxyapatite crystals which make up the inorganic component of bone. Trabecular bone is important to calcium turnover in bone as it presents with a greater surface area and so it is highly accessible. Bone mineralisation and resorption are regulated by PTH and vitamin D in contrast to calcitonin which stimulates bone formation only (Blair *et al*., 2007).

PARATHYROID HORMONE ACTIONS AND CALCIUM REGULATION

PTH, secreted by chief cells in the parathyroid glands is essential in regulating calcium and phosphate levels in the body by influencing intestinal absorption, renal excretion as well as ion exchange between the extracellular fluid and bone fluid across the osteocytic membrane. Maximal PTH secretion occurs at calcium levels <3.5 mg dL^{-1} and is inhibited at levels >5.5 mg dL^{-1}. In low calcium levels, adenylyl cyclase is activated causing an increase in intracellular cyclic AMP. Phospholipase C is inhibited causing a decrease in inositol triphosphate and in turn, a decrease in intracellular calcium. These processes stimulate high levels of PTH secretion.

PTH causes bone absorption of calcium and phosphate from bone by two ways; activating osteocytes and osteoblasts within minutes to hours and stimulating haematopoeitic tissue for osteoclast proliferation. After a few days, secondary signals activate the fully matured osteoclasts to increase reabsorption of bone itself and not selectively taking up calcium and phosphate ions from the bone reservoir. Absorption of salts takes place readily; since they are extremely small and have a high surface area exposed to extracellular fluid and blood (about 5% of the cardiac output is distributed to bone). PTH promotes the formation of vitamin D_3 in the kidneys and therefore, indirectly promotes calcium absorption through the gut. PTH prevents calcium excretion in the distal convoluted tubules in the kidneys by stimulating its reabsorption whose actions are mediated via the PTH receptor. Mutations in the PTH receptor cause problems such as hypocalcemia and Jansen's metaphyseal chondrodysplasia amongst others, showing how important PTH intracellular mechanisms are to calcium homeostasis.

PTH also increases inorganic phosphate elimination by the kidneys by inhibiting its reabsorption in the distal tubules of the kidneys (Pettway *et al*., 2007). The red lines indicate feedback inhibition of parathyroid hormone and 1α-hydroxylase whilst the green positive sign and red negative sign show enhancement and inhibition of

Corresponding Author: Renald Blundell, Department of Physiology and Biochemistry, University of Malta, Msida, Malta

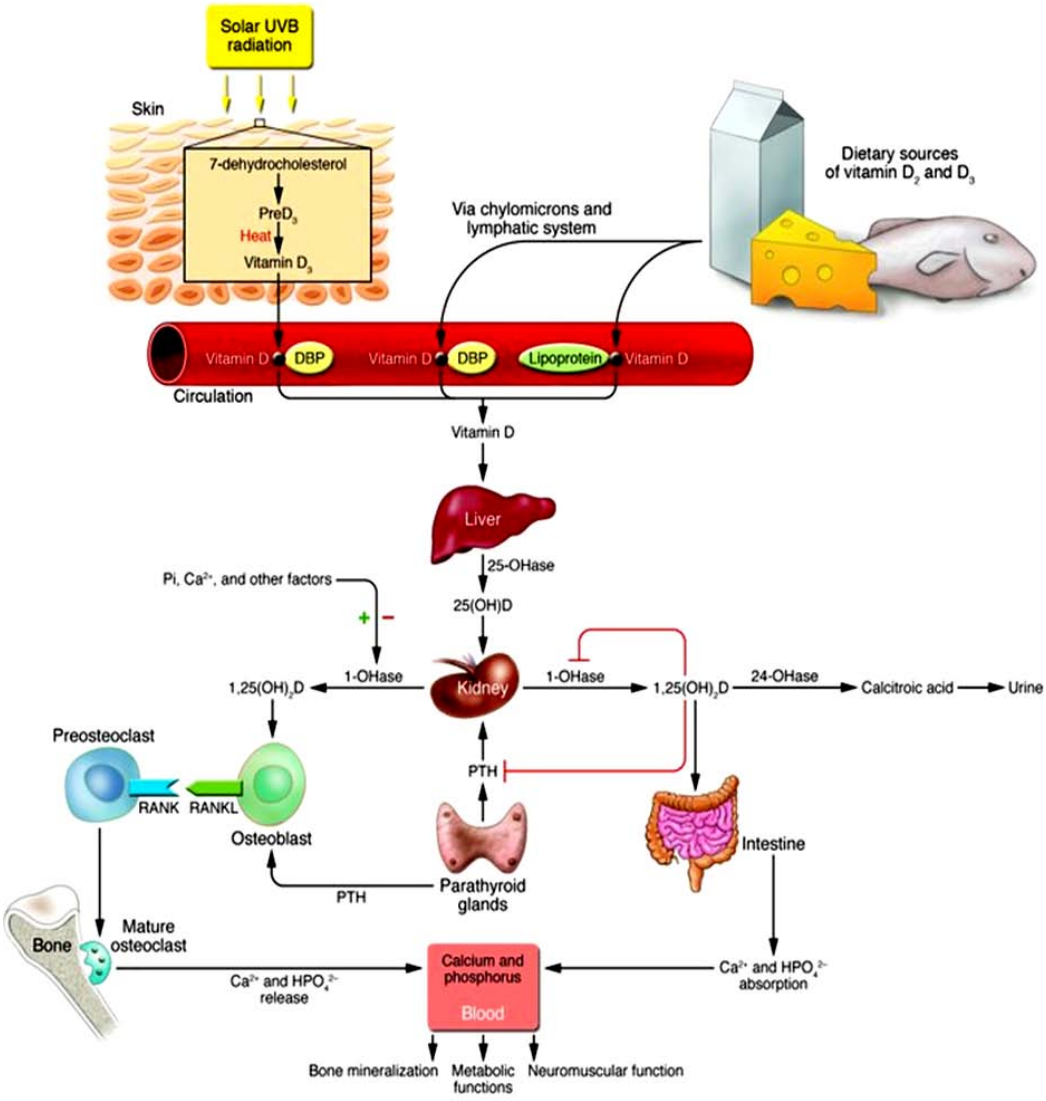

Fig. 1: The main processes of vitamin D synthesis, metabolism and its effects on the intestine and bone in conjunction with PTH

1α-hydroxylase. Receptor activator for nuclear kB (RANK) stimulates osteoclastic activity in bone (Fig. 1) (http://www.jci.org/articles/view/29449/figure/3). Continued PTH stimulation for months results in weakened bones, thus osteoblasts are activated simultaneously in an attempt to mineralise bone. Since, bone is a buffer-reservoir of calcium and contains about 1000 times as much calcium as the extracellular fluid, the effect of weakened bones is not immediately observed. However, in severe calcium deficiency or prolonged PTH secretion; commonly caused by vitamin D deficiency in children and the elderly, leading to secondary hyperparathyroidism, bone cavities containing multinucleated osteoclasts can be found after several months. The mitochondria of tissues such as the intestines are rich in calcium and also aid the buffering system as exchange across to the extracellular fluid occurs to maintain constant calcium levels (Pettway *et al*., 2007).

IDIOPATHIC HYPERCALCIURIA AND CALCIUM SENSING RECEPTORS

In a study by Worcester and Coe (2008), it was found that increased calcium bone loss results in Idiopathic Hypercalciuria (IH) which in turn causes kidney stones. Usually, in bones which are no longer growing in healthy non-pregnant adults, calcium absorption is matched by renal excretion. This is sufficient for the

maintenance of bone unless there is a pathological reason for excess excretion (i.e., >250 mg day^{-1} in females and >300 mg day^{-1} in males in urine). IH was found to be a complex polygenic trait which is largely dependent on the diet. It was found that a low calcium diet results in a negative calcium balance despite increased intestinal uptake and decreased renal excretion in IH. The continual loss of calcium from resorption is a detriment to the skeletal system and growth. This condition also causes an increase in VDR receptors however, there is no significant increase in 1,25-$(OH)_2D_3$ which could point to increased effectiveness of 1,25-$(OH)_2D_3$ due to increased receptors. Calcium Sensing Receptors (CaSR) responsive to 1,25-$(OH)_2D_3$ and located in parathyroid, renal, bone and intestinal tissues in these patients were found to be mutated having a gain in function. This abnormality along with VDR polymorphisms is considered to be a contributing factor to the disease. PTH levels in these patients were normal or slightly low however, PTH seems to be suppressed therefore causing less calcium reabsorption from the late distal and collecting tubules.

INTRACELLULAR PTH MEDIATED MECHANISMS

Cyclic AMP seems to mediate most of PTH's effects by a secondary messenger mechanism since, it increases rapidly in its effecter cells including osteocytes and osteoclasts. Osteoclastic secretion of enzymes and acids which cause bone resorption and formation of 1,25-$(OH)_2D_3$ may be dependent on cAMP mechanisms. A slight decrease in calcium detected by the CaSRs in the parathyroid glands causes an immediate increase in secretion of PTH and the opposite occurs in an increase in calcium serum concentration (Guyton and Hall, 2005). Osteoclasts also possess a calcium sensing function when a fluctuation of as much as 8-20 mM is detected, hydroxyapatite dissolution occurs by stimulated osteoclasts. The Ryanodine Receptor molecule (RyR) seems to aid osteoclast regulation when it comes to calcium influx and efflux and possibly calcium sensing, however its role remains unclear (Blair *et al*., 2007).

OPG/RANK/RANK-L SYSTEM AND BONE REMODELLING

A protein belonging to the Tumour Necrosis Factor superfamily, RANK-L (receptor activator nuclear factor kB ligand), its receptor RANK (receptor activator nuclear factor kB) and Osteoprotegerin (OPG) seem to play a key role in bone resorption. RANK is a receptor found on osteoclasts, RANK-L is transcribed by osteoblasts, bone marrow stromal cells and T-lymphocytes and OPG is expressed on osteoblasts. PTH and vitamin D seem to be involved in OPG and RANK-L regulation and expression on cells, consequently regulating bone remodelling. Remodelling occurs in steps including activation, resorption, reversal and formation. Although, OPG numbers increase in people >70 years of age, the OPG/RANK/RANK-L mechanisms involved in preventing bone loss deem to be insufficient. PTH in the elderly is increased resulting in increased calcium in the extra- and intra-cellular fluid.

However, these patients are usually suffering from vitamin D hypovitaminosis due to a reduction in amount of 7-dehydrocholesterol in the skin required for vitamin D synthesis as well as more time spent indoors with insufficient exposure to UV light and low vitamin D (and calcium) intake in the diet (Kearns *et al*., 2008).

CALCITONIN REGULATING CALCIUM AND PHOSPHATE LEVELS

Calcitonin has the opposite effects of PTH as it depresses calcium concentration in the extracellular fluid. It is secreted by the parafollicular cells (C cells) in the follicles of the thyroid gland in response to increased calcium levels. Therefore, it inhibits the absorptive action of osteoclasts as well as osteolytic activities and amorphous calcium phosphate exchange across the osteocytic membrane. Consequently, it deposits excess calcium in the form of calcium salts. A long term effect of calcitonin is to decrease osteoclast formation resulting in decreased osteoblast numbers and it exchanges calcium despite laying down mineral salts on the bone matrix. However, calcitonin has a limited effect on calcium homeostasis, since studies have shown that following a thyroidectomy, the calcium ion concentration is not significantly changed. The rates of absorption and deposition are very low in humans, thus decreased absorption due to calcitonin does not impact extracellular calcium concentration unless a pathological condition is present such as Paget's disease in which osteoclasts are highly activated. Also as calcitonin increases, PTH decreases and vice versa (Davey *et al*., 2008).

CONCLUSION

Both PTH and calcitonin work in influencing calcium and phosphate levels and are released depending on the activation of the calcium sensitive cells. These hormones affect each other as well as vitamin D and maintain calcium within a narrow range. A loss of control in calcium levels is detrimental as can be seen in conditions such as idiopathic hypercalciuria, primary hyperparathyroidism, pseudohypoparathyroidism, hypercalcemia due to malignancy and Jansen's metaphyseal chondrodysplasia where a PTH receptor defect is involved.

REFERENCES

Blair, H.C., P.H. Schlesinger, C.L. Huang and M. Zaidi, 2007. Calcium signalling and calcium transport in bone disease. SubCell. Biochem., 45: 539-562.

Davey, R.A., A.G. Turner, J.F. McManus, W.S.M. Chiu and F. Tjahyono *et al*., 2008. Calcitonin receptor plays a physiological role to protect against hypercalcemia in mice. J. Bone Mineral Res., 23: 1182-1193.

Guyton, A.C. and J.E. Hall, 2005. Textbook of Medical Physiology. 11th Edn., Elsevier, Philadelphia, USA., ISBN-13: 978-0-7216-0240-0.

Kearns, A.E., S. Khosla and P.J. Kostenuik, 2008. Receptor activator of nuclear factor êB ligand and osteoprotegerin regulation of bone remodeling in health and disease. Endocr. Rev., 29: 155-192.

Pettway, G.J., J.A. Meganck, A.J. Koh, E.T. Keller, S.A. Goldstein and L.K. McCauley, 2007. Parathyroid hormone mediates bone growth through the regulation of osteoblast proliferation and differentiation. Bone, 42: 806-818.

Worcester, E.M. and F.L. Coe, 2008. New insights into the pathogenesis of idiopathic hypercalciuria. Semin. Nephrol., 28: 120-132.