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CALCIUM HOMEOSTASIS

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Calcium is an essential ion within the human body. The maintenance of a constant free ionised calcium concentration is biologically important for the function of excitable tissues. Abnormalities in serum calcium values may have profound effects on neurological, gastrointestinal and renal function. Normal calcium concentrations are maintained as a result of tightly regulated ion transport by the kidneys, intestinal tract and bone. This is mediated by calcaemic hormones, in particular parathyroid hormone and the active form of Vitamin D. Changes in calcium transport resulting in movement into or out of the extracellular fluid will lead to hypercalcaemia, respectively. In this article the mechanisms responsible for calcium homeostasis will be reviewed.

Calcium balance

Calcium is an important nutrient. The daily intake is approximately 1000mg/day, about the amount of one litre of milk. The adult human body contains approximately 1100g (27.5mol) of calcium. 99% of the calcium is in bone. Blood calcium levels are normally 9-10.2mg/dL (2.25-2.55mmol/L). Of the total amount, 50% is free ionised calcium, 10% is combined with various anions (including bicarbonate, citrate, phosphate, lactate and sulphate) and the remaining 40% is bound to serum proteins mainly albumin. Free ionised calcium is the physiologically important component of the total calcium. In plasma, the ionised calcium concentration is normally maintained within a tight range (1.0-1.25mmol/l).

Intestinal absorption

30-80% of ingested calcium is absorbed, primarily in the upper small intestine. Absorption is related to calcium intake. If intake is low, active transcellular calcium transport in the duodenum is increased and a larger proportion of calcium is absorbed by the active process compared with the passive paracellular process that occurs in the jejunum and ileum.

Vitamin D is important for the active process. Active calcium transport depends on the presence in the intestinal cell of calbindin D9K, the biosynthesis of which is totally dependent on vitamin D. Passive absorption in the jejunum and ileum predominates when dietary calcium intake is adequate or high.

Calcium reaching the large intestine is absorbed by active and passive processes. Usually, no more than 10% of total absorption takes place in the large intestine, but this site becomes nutritionally important in conditions of significant small bowel resection.

Calcium absorption is inhibited by phosphates and oxalates because these anions form insoluble salts with calcium in the intestine.

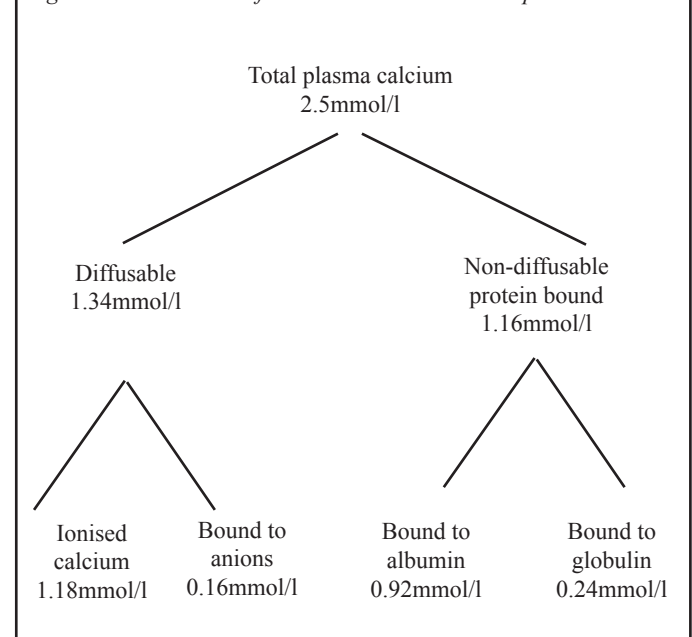
Physiological functions of calcium

Calcium plays a central role in a number of physiological processes that are essential for life. Calcium is necessary for several physiological processes including neuromuscular transmission, smooth and skeletal muscle contraction, cardiac

automaticity, nerve function, cell division and movement, and certain oxidative processes. It is also a co-factor for many steps during blood coagulation. Intracellular calcium is involved as a second messenger in many intracellular responses to chemical and electrical stimuli and required by many enzymes for full activity. Many different calcium binding proteins have been described, but the two with well established functions are troponin and calmodulin. Troponin is involved in muscle contraction, whereas calmodulin causes configurational changes to proteins and enzyme activation.

Intracellular calcium levels are much lower than the extracellular, due to relative membrane impermeability and membrane pumps employing active transport. Calcium entry via specific channels leads to direct effects, e.g. neurotransmitter release in neurones, or further calcium release from intracellular organelles, e.g. in cardiac and skeletal muscle.

Figure 1: Distribution of calcium in normal human plasma



Influences on calcium concentrations

Total plasma calcium values vary with the plasma concentration. Since a significant proportion of calcium in the blood is bound to albumin, it is important to know the plasma albumin concentration when evaluating the total plasma calcium. In general, 0.2mmol/L must be added to the total calcium concentration for each 1g/dL decrease in albumin concentration from the normal 40g/dL. However, this relationship between albumin and calcium is less reliable in critically ill patients. Ionized calcium increases with acidosis, and decreases with alkalosis. Therefore, for each 0.1 decrease in pH, ionised calcium rises by about 0.05mmol/L. In order to ensure accurate measurement of calcium concentrations, blood should be taken without a tourniquet, and without hyper- or hypoventilation.

Regulation of calcium homeostasis

Three principal hormones are involved in calcium homeostasis, acting at three target organs, the intestine, bone and kidneys:

1 Vitamin D

Vitamin D is a group of closely related sterols produced by the action of ultraviolet light. Vitamin D₃ (cholecalciferol) is produced by the action of sunlight and is converted to 25-hydroxycholecalciferol in the liver. The 25-hydroxy-cholecalciferol is converted in the proximal tubules of the kidneys to the more active metabolite 1,25-hydroxy-cholecalciferol. 1,25-hydroxycholecalciferol synthesis is regulated in a feedback fashion by serum calcium and phosphate. Its formation is facilitated by parathyroid hormone.

The actions of Vitamin D as follows:

1. Enhances calcium absorption from the intestine
2. Facilitates calcium absorption in the kidney
3. Increases bone calcification and mineralization
4. In excess, mobilises bone calcium and phosphate

2. Parathyroid hormone (PTH)

Parathyroid hormone is a linear polypeptide containing 84 amino acid residues. It is secreted by the chief cells in the four parathyroid glands. Plasma ionized calcium acts directly on the parathyroid glands in a feedback manner to regulate the secretion of PTH. In hypercalcaemia, secretion is inhibited, and the calcium is deposited in the bones. In hypocalcaemia, parathyroid hormone secretion is stimulated. The actions of PTH are aimed at raising serum calcium.

1. Increases bone resorption by activating osteoclastic activity
2. Increases renal calcium reabsorption by the distal renal tubules
3. Increases renal phosphate excretion by decreasing tubule phosphate reabsorption
4. Increases the formation of 1,25-dihydrocholecalciferol by increasing the activity of alpha-hydroxyls in the kidney

A large amount of calcium is filtered in the kidneys, but 99% of the filtered calcium is reabsorbed. About 60% is reabsorbed in the proximal tubules and the remainder in the ascending limb of the loop of Henle and the distal tubule. Distal tubule absorption is regulated by parathyroid hormone.

3. Calcitonin

Calcitonin is a 32 amino acid polypeptide secreted by the parafollicular cells in the thyroid gland. It tends to decrease serum calcium concentration and, in general, has effects opposite to those of PTH. The actions of calcitonin are as follows:

1. Inhibits bone resorption
2. Increases renal calcium excretion

The exact physiological role of calcitonin in calcium homeostasis is uncertain.

The calcium-sensing receptor (CASR)

This receptor has recently been cloned. It is a G protein-coupled receptor that plays an essential part in regulation of extracellular calcium homeostasis. This receptor is expressed in all tissues related to calcium control, i.e. parathyroid glands, thyroid C-cells, kidneys, intestines and bones. By virtue of its ability to sense small changes in plasma calcium concentration and to couple this information to intracellular signalling pathways that modify PTH secretion or renal calcium handling, the CASR plays an essential role in maintaining calcium ion homeostasis.

Bone and calcium

The calcium in bone exists in two forms: a readily exchangeable pool and a much larger reservoir of stable calcium, which is about 0.5 to 1% of the total calcium salts and is the first line of defence against changes in plasma calcium. It provides a rapid buffering mechanism to keep the serum calcium ion concentration in the extracellular fluids from rising to excessive levels or falling to very low levels under transient conditions of excess hypavailability of calcium. The other system is mainly concerned with bone remodelling by the constant interplay of bone resorption and deposition, which accounts for 95% of bone formation.

Effects of other hormones on calcium metabolism

Glucocorticoids lower serum calcium levels by inhibiting osteoclast formation and activity, but over long periods they cause osteoporosis by decreasing bone formation and increasing bone resorption. They also decrease the absorption of calcium from the intestine by an anti-vitamin D action and increased its renal excretion. The decrease in serum calcium concentration increases the secretion of parathyroid hormone, and bone resorption is facilitated. Growth hormone increases calcium excretion in the urine, but it also increases intestinal absorption of calcium, and this effect may be greater than the effect on excretion, with a resultant positive calcium balance. Thyroid hormones may cause hypercalcaemia, hypercalciuria, and, in some instances, osteoporosis. Oestrogens prevent osteoporosis, probably by a direct effect on osteoblasts. Insulin increases bone formation, and there is significant bone loss in untreated diabetes.

Key points in calcium homeostasis

- Calcium homeostasis is regulated by three hormones, parathyroid hormone, vitamin D and calcitonin. The free, ionised calcium concentration is physiologically important for the functions of excitable tissues such as nerve and muscle.
- Parathyroid hormone increases plasma calcium by mobilising it from bone, increases reabsorption from the kidney and also increases the formation of 1, 25 dihydrocholecalciferol.
- 1,25-dihydrocholecalciferol increases calcium absorption from the intestine, mobilises calcium from the bone and increases calcium reabsorption in the kidneys
- Calcitonin inhibits bone resorption and increases the amount of calcium in the urine, thus reducing plasma calcium
- The calcium-sensing receptor (CASR) plays an important role in regulation of extracellular calcium.

Clinical Implications for the Anaesthetist Perioperative period

Dysfunctional states

Any abnormalities in serum calcium should be corrected pre-operatively. The main risk in anaesthetising patients with either hypo or hypercalcaemia is cardiac dysrhythmias.

Hypocalcaemia

Hypocalcaemia may present with acute symptoms or be asymptomatic. Clinical signs include tetany, carpopedal spasm and laryngeal stridor. It may occur in hypoparathyroidism, vitamin D deficiency, phosphate excess and acute pancreatitis. Hypocalcaemia may lead to cardiac dysrhythmias, decreased cardiac contractility, causing hypotension, heart failure or both. Electrocardiographic changes include prolongation of the QT interval. Hypocalcaemia may be accompanied by changes in magnesium concentrations.

Hypocalcaemia can occur following rapid administration of citrated blood or lavage volumes of albumin and in alkalosis caused by hyperventilation. Transient hypocalcaemia may also be seen following heparin, protamine or glucagons administration.

Acute hypocalcaemia can also occur in the immediate post-operative period, following removal of the thyroid or parathyroid glands. It may present as laryngospasm and re-intubation of the trachea may be required. Administration of intravenous calcium is needed to occur acute hypocalcaemia.

Hypercalcaemia

Hypercalcaemia may present with renal problems, polyuria and polydipsia, neuropsychiatric disorders, nausea, vomiting and peptic ulceration. The cardiovascular effects include raised blood pressure, a shortened Q-T interval and dysrhythmias.

Causes of hypercalcaemia include hyperparathyroidism, malignancy, drug therapy such as thiazides and lithium, and immobilisation. Specific treatment is aimed at the cause, but it may also be necessary to decrease calcium levels by increasing excretion and decreasing bone resorption. Frusemide, rehydration, calcitonin and intravenous phosphate buffers can be used to decrease serum calcium.

Neuromuscular transmission

Calcium plays an important role in neuromuscular transmission and muscle contraction. The interaction of calcium with muscle relaxants is complex and unpredictable. Although calcium facilitates the release of acetylcholine from the motor nerve terminal, it also stabilizes the post-junctional membrane. Overall, response to non-depolarising muscle-relaxants is potentiated by both hypo and hypercalcaemia.

Magnesium sulphate, used for the treatment of pre-eclampsia and eclampsia may cause muscle weakness by inhibiting the release of acetylcholine from the nerve terminal. Intravenous calcium will antagonize this effect.

Many antibiotics such as aminoglycosides, polymyxins, tetracyclines, lincomycin and clindamycin cause potentiation

of neuromuscular block by nondepolarising muscle relaxants. Several mechanisms have been postulated to explain the variety of antibiotics that can cause such a block. One mechanism is thought to be an inhibition of the pre-junctional release of acetylcholine, which can be reversed by administering calcium. This is especially useful in the case of aminoglycoside antibiotics.

Massive blood transfusion

During massive blood transfusion, hypocalcaemia can occur due to binding of calcium by citrate preservative in the stored blood. Clinically significant hypocalcaemia resulting in dysrhythmias and hypotension does not occur in normal situations unless the transfusion rate exceeds one unit every five minutes. The citrate in the transfused blood is metabolised in the liver. Patients with hepatic dysfunction or hypothermia may require calcium infusion during massive transfusion.

Malignant hyperthermia

Malignant hyperthermia is a rare, autosomal dominant disorder, characterised by an acute hypermetabolic reaction caused by exposure to succinylcholine and volatile agents. Clinical features include unexplained tachycardia, hypercapnia, skeletal muscle rigidity, labile blood pressure, cyanosis, mottling of the skin and high body temperature.

The basic abnormality is an increase in cytoplasmic calcium ion concentration. The ryanodine receptor is a calcium efflux channel located on the sarcoplasmic reticulum. It modulates calcium release from channels in the sarcoplasmic reticulum. Abnormalities in the structure and function of this receptor are thought to be involved in the pathogenesis of malignant hyperthermia. Increased cytoplasmic calcium concentration results in prolonged actin and myosin interaction and irreversible contracture. This leads to increased O₂ consumption and CO₂ production. Dantrolene sodium is the drug of choice in the treatment of malignant hyperthermia and it acts by inhibiting calcium ion release from the sarcoplasmic reticulum.

The role of calcium cardiopulmonary resuscitation (CPR)

Calcium plays a central role in cardiac contraction. In the past, it was used as an inotropic agent during cardiopulmonary resuscitation (CPR). There is no scientific evidence to suggest that calcium has any benefits in the treatment of ventricular fibrillation or asystole. On the contrary, there is evidence that high plasma concentrations achieved following intravenous calcium administration during CPR could have deleterious effects on ischaemic myocardium and may delay cerebral recovery. It has been shown that calcium which accumulated excessively in the myocardium during arterial reperfusion after a period of relative ischaemia, led to cell death. Calcium is no longer recommended for universal management of CPR. Calcium is only indicated in CPR if there is:

- Severe hypocalcaemia
- Hyperkalaemia
- Myocardial depression resulting from calcium channel blocking drugs

Conclusion

In summary, calcium has an important physiological role in the conduct of anaesthesia. Meticulous attention should be paid to maintain serum calcium within the physiological limits and to treat any abnormality resulting from calcium imbalance.

References

Guyton AC. Parathyroid Hormone, Calcitonin, Calcium and phosphate metabolism, Vitamin D, Bone and Teeth. Text Book of Medical Physiology;2001:899-915.

Bushinsky DA, Monk RD. Calcium. Lancet 1998;352:306-311

Aguilera M, Vaughan RS. Calcium and the anaesthetist. Anaesthesia 2000;55:779-790.

Hendy GN, D'souza-Li L, Yang B, Canaff L, Cole D. Mutations of the calcium-sensing receptor (CASR) in familial hypocalciuric hypercalcaemia, neonatal severe hyperparathyroidism, and autosomal dominant hypocalcaemia. Human Mutation 2000;16:281-296.

Bronner F, Pansu D. Nutritional aspects of calcium absorption. Journal of Nutrition 1999;129:9-12.
