International Journal of Research in Engineering, Science and Management
Volume 5, Issue 7, July 2022
https://www.ijresm.com | ISSN (Online): 2581-5792

Effects of Chronic Stress on Hypocalcaemic Tetany

Sairam Ravi*
Student, Year 12, GEMS Jumeirah College, Dubai, United Arab Emirates

***Abstract*: This article is written with the aim of integrating the role of chronic stress, along with its effects on neuroendocrinal physiology, on the pathogenesis of tetany. This encompasses the different underlying mechanisms of development, e.g., hypocalcaemia, hypomagnesaemia, hyperphosphataemia (i.e., electrolyte disorders), improper endocrine function as well as a brief analysis of corresponding aetiologies. This paper discusses the effects of psychological stress in the long term, i.e., chronic stress, which has been known to contribute to the development of a variety of medical conditions in the human body. The study has suggested, apart from correlations, indirect causal mechanisms between chronic stress and the rate of development of a disease. The findings made show that in multiple cases, chronic stress can contribute to the processes of a condition's pathogenesis, being an accelerating factor in its development. However, the review of scientific literature available only indicates an aggravation of tetanic physiology in the presence of chronic stress, as opposed to the latter being a primary aetiological factor. The involuntary contractions and spasms seen collectively in tetany are primarily associated with underlying electrolytic imbalances or vitamin disorders (including calcium, magnesium and Vitamin D deficiencies), the pathophysiology of which will be discussed in further depth in this review paper. However, these disorders may themselves be accelerated during development by chronic stress, which consists of neurological cortisol mechanisms that can influence the action potential frequencies of neurons and muscle cells. Analyzed further are the spasms caused by the under function of endocrine glands, namely the parathyroid glands, which are also linked to regulation of calcium and phosphate levels – this, in turn, can be affected as a part of neurological changes that may be aided by chronic stress. Therefore, the neurological aspects of improper electrolyte-PTH interplay, which may contribute to the development of tetanic seizures, is discussed. The methodology utilized in this review paper includes the anatomization of multiple research papers in the field and medical case studies from verified sources – specific information from these studies may be presented in the form of images/labelled diagrams or tables for further analysis and understanding.**

***Keywords*: Tetany, Chronic stress, Hypocalcaemia, Hypomagnesaemia, Hyperphosphataemia, Vitamin D deficiency.**

1. Introduction

Tetany is a condition that is primarily typified by the involuntary contractions of body muscles, i.e., muscular spasms. Resulting from increased neuromuscular activity and negative (i.e., impairment of a type of sensory perception) or positive (i.e., abnormal hypersensitivity to stimuli) symptoms associated with characteristic sensory disturbance, these movements may manifest in multiple forms [1], [2]. These include milder signs that may involve circumoral numbness, which is a negative symptom of absent or reduced sensory perception around the mouth. Muscle cramps may also be experienced, along with carpal and/or pedal paraesthesiae – these involve abnormal sensations at the distal points of the body [3]. More serious symptoms of tetany include spasms of the voice box, laryngospasms, which may also indicate a consequent development of spasmodic dysphonia/laryngeal dystonia. Severe cases of tetany have, in the past, involved patients presenting with seizures or specific forms of myocardial dysfunction [4].

Tetanic spasms and cramps are usually associated with a significant calcium deficiency, i.e., hypocalcaemia. Tetany is also known to be caused by an underlying presence of hypomagnesaemia, hyperphosphataemia (electrolyte disorders) or improper endocrine function (e.g., hypoparathyroidism) [5]. The mechanistic pathogenesis and pathophysiology of these underlying conditions will be discussed in further depth later in this article. These, however, have been shown to be induced or contributed to by chronic psychological stress, the neurological effects of which can impact physiological factors that increase the action potential frequencies of muscle cells or neurones.

Studies from research in the field have repeatedly proven causal mechanisms that link chronic stress, along with its secondary results (e.g., anxiety), and the pathophysiological processes of neuromuscular and neuroendocrinal disorders. The effects of elevated cortisol levels have been investigated, with many observations in relation to neuronal auto receptors, neurotransmission and action potential frequencies being made. These collective changes to the functioning of the neurological system, in the long term, pose significant problems to endocrine and muscular function.

If the underlying mechanisms linking chronic stress with neuromuscular and neuroendocrinal activity are understood, the diagnostic and prognostic aspects of tetany can be analyzed more effectively. Therefore, the exact progression of treatment methods can be visualized in greater depth, along with being modified to involve minimization of psychological stress by considering lifestyle factors.

*Corresponding author: sairav1005@gmail.com

2. Tetanic Pathogenesis

The pathogenesis of tetany involves hypocalcaemia - this itself may be induced by the array of other aetiological factors, including hypomagnesaemia. The chronological mechanisms by which low calcium levels can lead to the multitude of symptoms in tetany patients will be covered when discussing tetanic pathophysiology in a dedicated section. If the processes through which other factors can result in hypocalcaemia are enumerated, their impact can better be understood before attributing them to the relevant neurophysiological aspects of chronic stress.

A. Hyperphosphataemia

Defined as a condition wherein the blood serum phosphate concentration is greater than 4.5 mg dL^{-1}, hyperphosphataemia is classed as an archetypal electrolyte disorder that influences blood serum calcium levels. Severe hyperphosphataemia is usually characterized by a blood serum phosphate concentration of 14 mg dL^{-1} and above [6]. Both the hydrogen phosphate (HPO_4^{2-}) anion and the dihydrogen phosphate ($H_2PO_4^-$) anion are present in considerable levels within the blood serum, their exact ratio being difficult to determine. Therefore, the values discussed will truly refer to the concentration of inorganic phosphorus, which occupies a relatively narrow normal range from 3 to 4 mg dL^{-1} in adults and 4 to 5 mg dL^{-1} in children [5].

1) Phosphate homeostasis

Active absorption of ingested phosphate in the small intestine occurs through Type IIB sodium-dependent phosphate co-transporter proteins (Na^+P_i-2b), while reabsorption on the luminal side of the proximal tubule takes place through Type IIA sodium-dependent phosphate co-transporter proteins (Na^+P_i-2a). There are three key elements, discussed below, that influence the processes of uptake and removal of serum phosphate.

- Calcitriol, which is otherwise known as 1,25-dihydroxycholecalciferol, is the active form of Vitamin D which increases the activity of the co-transporters [10], intestinal calcium absorption, bone resorption and fibroblast growth factor 23 (FGF-23) synthesis – it also suppresses PTH production [12].
- FGF-23, a phosphatonin, inhibits renal tubular reabsorption of phosphate by binding to the FGFR1-β-Klotho complex, with α-Klotho being a co-receptor – this reduces the expression of Na^+P_i-2a proteins [13] [14]. The phosphatonin is also known to decrease levels of calcitriol by reducing the expression of 1-alpha-hydroxylase, the enzyme responsible for the PTH-stimulated Vitamin D conversion mentioned below.
- Parathyroid hormone (PTH) stimulates renal tubular calcium reabsorption, bone resorption and the conversion of 25-hydroxycholecalciferol (calcifediol), the hydroxylated form of Vitamin D_3, to calcitriol [11].

Therefore, calcitriol, parathyroid hormone and FGF-23 constitute a triad of feedback loops controlling phosphate homeostasis, a critical concept in understanding hyperphosphataemic contribution to hypocalcaemia.

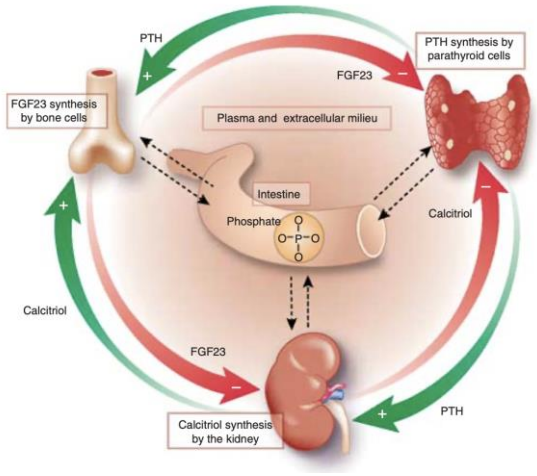

Fig. 1. Feedback loop triad responsible for phosphate homeostasis [10]

2) Elevation of blood serum phosphate concentration

Chronic renal failure is the most common cause of hyperphosphataemia – in this case, gastrointestinal absorption of phosphorus into the blood serum is maintained at the same rate. However, renal excretion is inhibited, leading to a net increase in the blood serum phosphate concentration.

Phosphate reabsorption into the blood serum by the proximal tubular Na^+P_i-2a co-transporters is regulated by the parathyroid hormone (PTH) and the fibroblast growth factor 23 protein (FGF-23). In the presence of hypoparathyroidism, the increased expression of NaPi-II co-transporters in the proximal tubule can lead to hyperphosphataemia [2] through impaired secretion of parathyroid hormone – this, in turn, is due to decreased activity of the four parathyroid glands. This directly results in a lowered rate of phosphorus excretion by the kidneys, leading to an elevated phosphate level in the blood serum. This can also be induced by a glomerular filtration of less than 30 ml min^{-1} and/or excessive delivery of phosphate(s) into the extracellular fluid due to use of phosphate enemas [8] [9] [15]. Retention of phosphates due to a lowered glomerular filtration rate (GFR) can further impair renal synthesis of calcitriol ($1,25(OH)_2D$). The elevated phosphate concentration can increase fibroblast growth factor 23 protein (FGF-23) levels and stimulate parathyroid hormone secretion.

In the case of tumour lysis syndrome (TLS), the destruction of many neoplastic cells undergoing rapid proliferation occurs. This results in the release of intracellular phosphate pools during the process of tumour lysis, increasing the blood serum phosphate concentration [2].

The common effect of the elements of hyperphosphataemic aetiology is the depression in serum calcium level through the deposition of calcium phosphate in bone or soft tissue [7], inhibition of the calcaemic response of bone to parathyroid hormone (PTH) and augmentation of the hypocalcaemic action of calcitonin. Due to acute kidney injury (AKI) because of tumour lysis syndrome, metastatic deposition can occur in the kidney, increasing the likelihood of renal failure and a positive feedback cycle of increasing phosphate concentration.

Elevated phosphate levels have also been shown to inhibit

synthesis of 1-alpha-hydroxylase, which leads to a lower activation rate of Vitamin D in the form of calcitriol – this decreases calcaemic intestinal absorption and renal reabsorption, along with the impairment of bone mineralization. As seen in Figure 1, this reduction in calcitriol increases PTH secretion in the parathyroid glands, which may lead to secondary hyperparathyroidism. This change would usually be followed by a compensatory mechanism in which the produced PTH stimulates production of more calcitriol. However, this cannot occur in this case due to the excessively high phosphate levels inhibiting 1-alpha-hydroxylase synthesis.

B. Hypomagnesaemia

Essential for the maintenance of neuromuscular stability, energy metabolism and nervous tissue electrical potential, magnesium is a cofactor for multiple enzymes and is involved in major cellular processes [17]. It holds a vital role in bone formation and muscular contraction, signifying the importance of its regulation in the extracellular fluid. The normal range for the blood serum magnesium concentration is between 1.46 and 2.68 mg dL^{-1}. In the case where hypomagnesaemia indirectly induces hypocalcaemic tetany, the level of magnesium is significantly below 1.46 mg dL^{-1} [16]. The mechanisms by which hypomagnesaemia can induce hypocalcaemic tetany can be understood to the required detail only when regular homeostasis of magnesium is studied in similar depth.

1) Magnesium homeostasis

The concentration of ionized magnesium in the blood serum is controlled by mechanisms that primarily involve the intestines, kidneys and bones [18]-[21]. This is shown below in Figure 2 [27]. As multiple studies have previously shown, intestinal absorption of magnesium is closely balanced by renal excretion [22]-[24]. Even during temporary periods of magnesium deficit, the sourcing of magnesium from bone, which acts as a storage system, allows for serum levels to be maintained within a narrow range [25]. Intestinal absorption of magnesium occurs predominantly in the jejunum and distal small intestine (ileum), with a smaller percentage of uptake taking place in the colon [26].

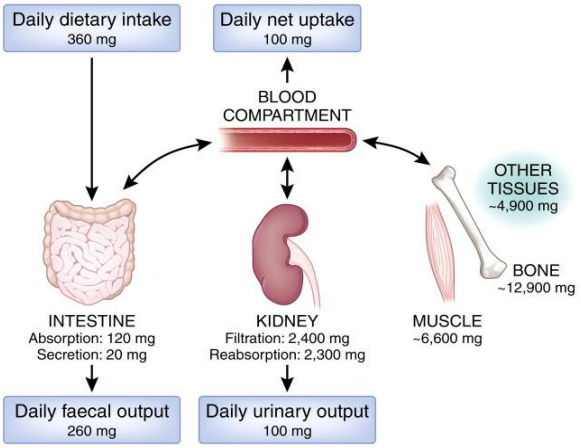

Fig. 2. Overview of magnesium absorption, storage and excretion [27]

The uptake of magnesium, illustrated in Figure 3, can occur in the intestines through two distinct absorption pathways [28]:

- Paracellular transport – This is a passive mechanism characterized by the diffusion of magnesium ions into the blood through spaces between enterocytes (cells of the intestinal epithelium). It occurs without the use of energy generated from adenosine triphosphate (ATP), aided by a lumen-positive transepithelial voltage of ~+5 mV [30].
- Transcellular transport – This is an active mechanism, wherein magnesium ions are transported from the intestinal lumen into the enterocyte cytoplasm through transient receptor potential channel melastatin members 6 and 7 (TRPM-6 and TRPM-7) in the luminal membrane. The ions are then transported from the enterocyte cytoplasm into the blood through the cyclin and cystathionine β-synthase domain divalent metal cation transport mediator 4 (CNNM-4) on the basolateral membrane. Through CNNM-4, sodium ions (Na^+) are taken into the cell while Mg^{2+} is transported into the blood. The sodium concentration within the cell, which directly influences magnesium movement, is controlled by sodium removal through the sodium-potassium adenosine triphosphatase pump (Na^+/K^+-ATPase) and luminal membrane uptake through the epithelial amiloride-sensitive sodium channel (ENaC).

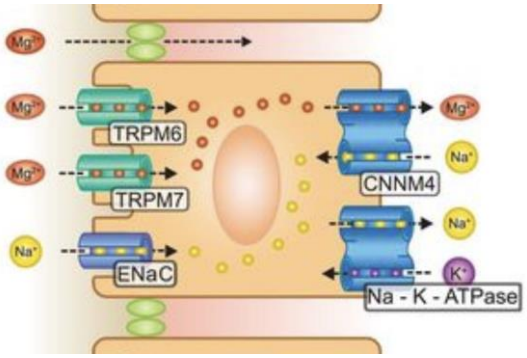

Fig. 3. Intestinal magnesium absorption pathways [29]

The intestinal absorption of Mg^{2+} is known to be regulated by several factors. Most importantly, studies have shown that calcitriol ($1,25(OH)_2D$) can increase the absorption of magnesium. Patients with chronic renal disease and associated hypomagnesaemia were treated with 2 mg day^{-1} of calcitriol for 7 days, resulting in the restoration of serum Vitamin D metabolite concentration from 0.9 (± 0.2) to 4.2 (± 0.6) ng dl^{-1}, i.e., an increase of 3.3 (± 0.8) ng dl^{-1}. The jejunal absorption of magnesium, which was determined using a triple-lumen constant-perfusion technique, was found to have risen from 0.04 (± 0.02) to 0.13 (± 0.02) ng dl^{-1}, i.e., an increase of 0.09 (± 0.04) ng dl^{-1} [31].

Of the ~2400 mg of magnesium normally filtered each day by the nephronal glomeruli, 95 – 99% is reabsorbed – this results in approximately 24 – 120 mg being excreted in the urine.

- Proximal tubule – Water is reabsorbed via aquaporin-1 proteins (AQP-1) situated in the

basolateral and luminal membranes, causing the luminal magnesium concentration to increase. When the transepithelial concentration gradient is sufficiently steep, Mg^{2+} reabsorption into the blood occurs in the process of passive paracellular diffusion.

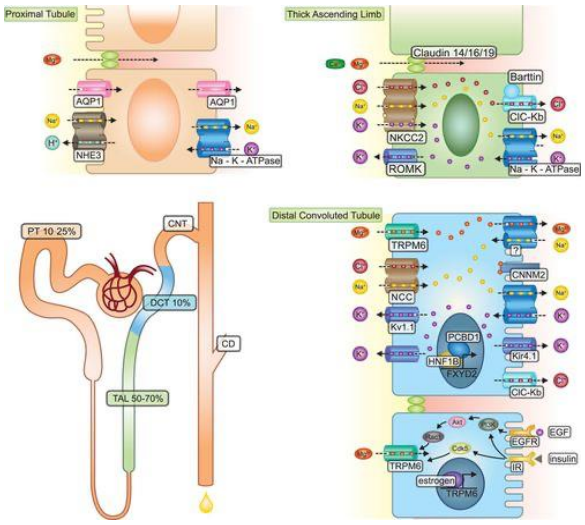

Fig. 4. Renal magnesium reabsorption pathways [29]

- Loop of Henle (mainly thick ascending limb) – A lumen-positive transepithelial potential difference gradient is created using mechanisms that involve Na^+, Cl^- and K^+ transport. Na^+ and Cl^- ions enter the cell cytoplasm through the apical furosemide-sensitive Na^+-K^+-$2Cl^-$ co-transporter (NKCC-2) in the luminal membrane. From here, the sodium ions are actively transported into the blood via the sodium-potassium adenosine triphosphatase pump (Na^+/K^+-ATPase). The chloride ions are also, through the voltage-gated chloride channel Kb (CLC-Kb), transported into the blood across the basolateral membrane. This, along with the recycling of potassium back into the lumen via the renal outer medullary K^+ (ROMK) channel, induces the lumen-positive voltage gradient required. The gradient, as expected, results in the diffusion of Mg^{2+} into the blood by the means of a passive paracellular transport mechanism – this occurs through claudins 14, 16 and 19 [32], [33].
- Distal convoluted tubule – Here, the transient receptor potential channel melastatin member 6 (TRPM-6) in the luminal membrane enables the uptake of Mg^{2+} into the cell cytoplasm [34]. Magnesium reabsorption into the blood occurs through an unidentified channel on the basolateral membrane.

With regards to renal magnesium reabsorption, the epidermal growth factor (EGF) comes across as an important regulator. EGF binds to the epidermal growth factor receptor (EGFR), initiating an intracellular cascade of mechanisms that up-regulate TRPM-6 activity [35]. Therefore, impaired EGF synthesis may contribute to hypomagnesaemia.

It must also be noted that magnesium mediates the inhibition of the outer medullary K^+ (ROMK) channel. Therefore, in the case of hypomagnesaemia, the reduced inhibition of ROMK activity may lead to increased excretion of potassium, contributing to the development of secondary hypokalaemia [36].

2) Elevation of blood serum magnesium concentration

A common cause of mild hypomagnesaemia is chronic inadequate dietary intake of magnesium. More significant cases, in the past, have been attributed to pathological conditions like anorexia nervosa [37].

Chronic renal conditions that impair absorption may also cause hypomagnesaemia, since multiple transport proteins involved may be impaired in function. It has been shown that metabolic acidosis, which can be a result of kidney damage, decreases the expression of TRPM-6 [38], increasing the loss of Mg^{2+} in the urine – this may eventually lead to hypomagnesaemia.

Recent research endeavors have also indicated that hypomagnesaemia may be induced by Type 2 diabetes mellitus. A study in 2017, carried out by S. Kurstjens et al. [39], used Pearson product-moment correlation coefficient (PPMCC) tests to determine the statistical relationships between diabetic variables and plasma Mg^{2+} concentration. Table 1 shows the relevant data. Around 30.6% of the 395 patients were found to have hypomagnesaemia. When comparing this to the 2% of people in a study of 5179 subjects, it can be concluded that hypomagnesaemia is clearly correlated with the incidence of Type 2 diabetes mellitus.

Statistically, the use of medication (PPI, metformin, insulin and β-adrenergic agonist) could explain less than 10% of the variation in magnesium concentration – this suggests that other factors are more strongly linked to hypomagnesaemia. As seen above, there is a negative correlation between the estimated glomerular filtration rate (eGFR) and the Mg^{2+} concentration. This can be explained by the occurrence of diabetic nephropathy, which results in glomerular hyperfiltration [40] – this elevated rate increases urinary loss of magnesium, reflecting the data above.

The positive correlation between insulin and Mg^{2+} concentrations can be explained by the fact that the former is known to enhance magnesium reabsorption in the thick ascending limb of Henle's loop [41]. Therefore, an insulin deficiency or resistance, as is present in Type 2 diabetes mellitus, can result in renal wasting of Mg^{2+} and consequent hypomagnesaemia.

The decreased ionized magnesium (Mg^{2+}) concentration seen in hypomagnesaemia result in decreased PTH secretion. This is observed from the lowered immunoreactive PTH levels in hypomagnesaemia and a rapid rise in plasma PTH when parenteral magnesium supplementation is administered [42]. Hypomagnesaemia can result in a decrease in adenyl cyclase generation of cyclic adenosine monophosphate (cAMP), a magnesium-dependent process. In turn, the release of PTH, which is contributed to by cAMP, is inhibited, leading to down-regulation of calcium and hypocalcaemia. Studies carried out in

isolated perfused bone have since demonstrated PTH resistance arising in the tissue, decreasing the rate of bone calcium resorption and turnover [43].

Table 1
Correlation data for plasma Mg^{2+} concentration and patient characteristics

Variable	PPMCC	*n*
Log_{10} triglycerides (mmol l^{-1})	-0.273	387
Log_{10} glucose (mmol l^{-1})	-0.231	383
eGFR (ml min^{-1})	-0.168	371
PPI	-0.084	0.094
Metformin	-0.268	-
Insulin	0.109	-
β-Adrenergic agonist	-0.103	-

It has also been shown that the saponification of magnesium in necrotic fat, which occurs in acute pancreatitis, can be responsible for hypomagnesaemia. However, it is important to recognize that the saponification of calcium, too, occurs in this case. Therefore, the hypomagnesaemia may only aggravate the hypocalcaemia through the lowering of PTH secretion and induction of end-organ PTH resistance [42].

C. Vitamin D deficiency

A deficiency of Vitamin D (hypovitaminosis D), especially its active hormonal form (calcitriol), is commonly associated with hypocalcaemia and consequent tetanic seizures.

1) Inadequate dietary intake of Vitamin D

In both children and adults, the lack of nutritional Vitamin D intake may be one of the major causes of a deficiency.

2) Inadequate sunlight absorption

A lowered synthesis rate of vitamin D in the skin can occur due to insufficient exposure to solar ultraviolet B radiation [44].

D. Parathyroid Hormone, Vitamin D and Bone Resorption

As described before, PTH and Vitamin D are required to initiate bone resorption, for which they stimulate osteoclast activity – however, this is done through the indirect mechanism shown below.

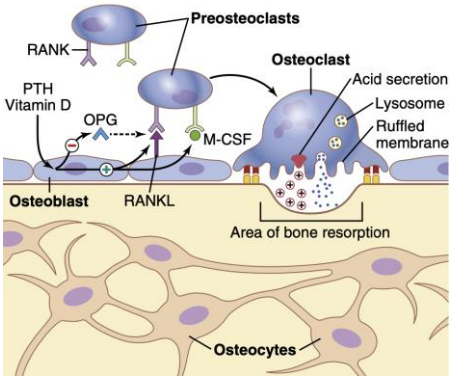

Fig. 5. PTH-Vitamin D-stimulated bone resorption mechanism [5]

PTH and Vitamin D receptors are not present on the osteoclasts. PTH, or Vitamin D, binds to a receptor on an osteoblast – this is shown above. This stimulates the synthesis of the receptor activator for nuclear factor κB ligand (RANKL), also known as the osteoprotegerin ligand (OPGL). The synthesized RANKL then binds to the RANK receptor on an osteoclast precursor – the latter is known as a preosteoclast. Osteoprotegerin (OPG), also called the osteoclastogenesis inhibitory factor, is responsible for the inhibition of preosteoclast differentiation (into a mature osteoclast) – Vitamin D and PTH, therefore, inhibit OPG production.

3. Tetanic Pathophysiology

Hypocalcaemic tetany remains the cornerstone of this article – as the possible aetiological factors involved in the pathogenesis have been assayed, the pathophysiology of tetany in relation to Ca^{2+} can now be studied.

Although calcium is considered an important factor for both neurotransmitter release and muscular contraction, hypocalcaemia leads to a paradoxical neuromuscular hyperexcitability. This counterintuitive mechanism must be understood to understand the physiological link between hypocalcaemia and tetany.

A. The Neuromuscular Role of Calcium

Intracellular Ca^{2+} is known to modulate multiple neuronal ion channels. Serum Ca^{2+} binds to the extracellular domain of some ion channels, resulting in allosteric modification of the gating behavior. The external Ca^{2+} may also influx into cells through calcium-permeable membrane proteins – these include voltage gated calcium channels (VGCCs), N-methyl-D-aspartate channels and acetylcholine nicotinic receptors [45].

A study in 2004 showed that a reduction of external calcium from 2 to 1 mM resulted in an increase of action potential frequency from 28 to 171 Hz in hippocampal neurones. The resting membrane potential rose from −67.5 to −64 mV, while the firing threshold fell from −59.3 to −63.3 mV [46]. It can be seen, from the reduced difference between the new values of resting potential and firing threshold, that making neuronal excitation very likely.

Neuronal resting membrane potential is approximately -70 mV. The transmembrane K^+ gradient is known to determine this potential – however, the reversal potential of K^+ is around -93 mV, creating a difference of ~20 mV. This is overcome by an Na^+ leak channel (NALCN), which provides a depolarizing current to establish neuronal stability [47]. External calcium, however, has been proven to shut the gating of NALCN, thereby reducing Na^+ current. This is done through a mechanism where Ca^{2+} binds to a calcium-sensing receptor (CaSR), inhibiting NALCN function – therefore, hypocalcaemia results in a lack of this down-regulation, giving rise to uncontrolled rise of resting membrane potential [48]. When this potential reaches a level close to the firing threshold, neuronal excitability increases, making involuntary muscular contractions more likely.

After depolarization and subsequent repolarization during an action potential, a small hyperpolarization occurs before membrane potential rises back to the firing threshold. This transient event is named the afterhyperpolarization (AHP), the amplitude of which determines the interspike interval duration between action potentials.

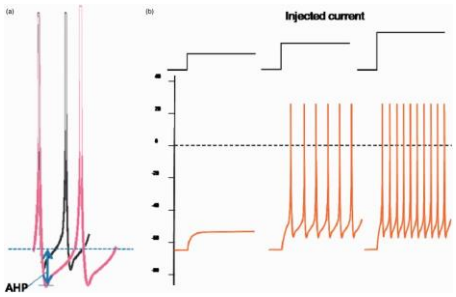

Fig. 6. AHP & effect of calcium current on action potential frequency [45]

It has been shown that calcium-activated potassium (KCa) channels may be responsible for controlling the magnitude of the AHP [49]. The KCa channels possess an intracellular domain to which Ca^{2+} binds, increasing K^+ outflow and, consequently, the AHP. In the presence of hypocalcaemia, there is a lowered calcium current through open VGCCs into the cell (during the action potential). Therefore, there is a lower incidence of Ca^{2+}-KCa binding, decreasing the number of activated KCa channels and, therefore, the AHP. This diminution of AHP magnitude, and so the interspike interval, causes an increase in action potential frequency.

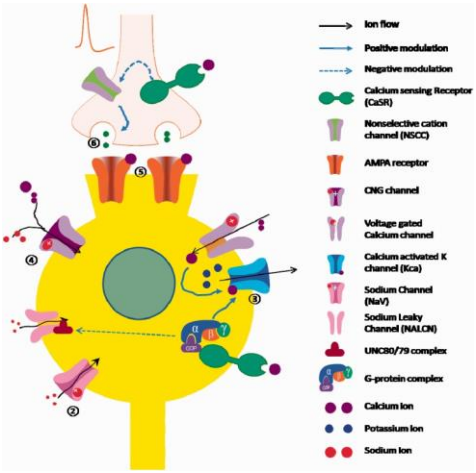

Fig. 7. Ion channels modulated by extracellular calcium [45]

4. Possible Roles of Chronic Stress

The associations and responses (e.g., anxiety) of chronic stress must also be considered to obtain an understanding of the latter's role in tetanic pathogenesis and pathophysiology.

A case report from 2011 [4] discusses the induction of acute hypocalcaemia in a patient due to hyperventilation – this stemmed from postoperative pain and anxiety in the post anaesthesia care unit (PACU). The sustained hyperventilation led to respiratory alkalosis and consequential hypocalcaemia, eventually producing tetanic carpal spasms. The collection of blood samples and the arterial blood gas (ABG) analysis that followed indicated a pH of 7.49, indicating respiratory alkalosis, and a low serum ionized calcium concentration of 0.70 mmol l^{-1}. Although the total serum calcium level was normal (9.6 mg dl^{-1}), the proportion of this in the ionized form was low. This illustrates the fact of hypocalcaemia, and its effects, being based around the level of ionized calcium.

Chronic stress can be triggered by a multitude of stimuli, often those that are recurrent or inherent parts of a patient's lifestyle and routine. This can be accompanied, in response, by chronic anxiety conditions like panic disorder (PD).

A 3-year study of 677 major depressive disorder (MDD) and panic disorder (PD) patients discovered that chronic stressors gave rise to a declining illness course and poorer treatment responses [50]. In a mouse study, chronic restraint and unpredictable stress caused the impairment of tonic inhibitory $GABA_A$ currents (i.e. regulatory mechanisms of neuronal excitability) in lateral amygdala projection neurones [51]. This impedes the usual magnitude of amygdala neuronal activity inhibition. Another mouse study exhibited an increase in glutamatergic excitability of basolateral amygdala neurones [52]. Both these neurobiological effects are known to increase the incidence of repeated panic attacks as a part of anxiety disorders [53].

Repeated periods of hyperventilation (i.e., rapid breathing with increased depth) accompanying and arising from panic attacks can be classed as a manifestation of chronic hyperventilation syndrome (CHVS), also known as dysfunctional breathing hyperventilation syndrome or central neuronal hyperexcitability syndrome (NHS). The high breathing rate causes a rise in the rate of respiration. Hypocapnia proceeds to develop, where the output of carbon dioxide in the lungs exceeds its metabolic production. This decreases the arterial partial pressure of carbon dioxide ($PaCO_2$), thereby increasing the ratio of bicarbonate / hydrogen carbonate (HCO_3^-) to $PaCO_2$. To restore equilibrium conditions, hydrogen ions (H^+) and hydrogen carbonate ions (HCO_3^-) circulating in the blood react with the aid of carbonic anhydrase catalysis. This forms a carbonic acid intermediate (H_2CO_3) that is converted into carbon dioxide and water as a compensation mechanism:

$$HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$$

As seen in the equation above, the concentration of hydrogen ions in circulation decreases, resulting in an increase in pH. In the case of chronic respiratory alkalosis, the proportion of body calcium that is protein-bound increases – this occurs alongside a corresponding decrease in ionized calcium levels, inducing hypocalcaemia and consequent tetanic spasms [2].

It has also been shown that chronic respiratory alkalosis can induce renal parathyroid hormone (PTH) resistance, hyperphosphataemia and hypocalcaemia. During a twelve-day period split equally between induced chronic respiratory alkalosis and recovery, the average $PaCO_2$ exhibited in four patients decreased by 8.4 mm Hg. This was accompanied by a 3.2 nmol l^{-1} decrease in hydrogen ion concentration, reflecting the rise in pH expected. Hyperphosphataemia was shown by a 0.14 mmol l^{-1} increase in PO_4^{2-} concentration, while hypocalcaemia was showcased by a 0.10 mmol l^{-1} decrease in ionized serum calcium [54].

It has been previously discussed that the saponification of magnesium and calcium in necrotic fat can occur as a part of acute pancreatitis pathophysiology. Interestingly, studies have

shown that chronic stress increases susceptibility to pancreatitis. Rats exposed to chronic restrain exhibited high levels of the cytokine tumour necrosis factor alpha (TNF- α), which is a known pro-inflammatory cytokine [55].

Stress is also known to activate the sympatho-adrenal-medullary (SAM) system and the hypothalamic-pituitary-adrenal (HPA) axis, which are both involved in stress response mechanisms. The resulting hyperactivity of cortisol, among other factors, exerts changes upon the hippocampus and negatively influences sleep [56].

Sleep deprivation, when sustained over a long period of time, showed effects that included impaired hepatic function and hyperphosphataemia [57]. This suggests that stress-induced insomnia may trigger processes associated with the developmental pathogenesis of hypocalcaemic tetany. However, exact causal mechanisms for this have not yet been proposed.

5. Conclusion

Hypocalcaemic tetany, on analysis, proves to be a condition with many possible aetiological factors. However, it is clear that most of these underlying mechanisms involve the interplay between parathyroid hormone (PTH), phosphate, magnesium and Vitamin D. They do not seem to instantaneously lead to chronic hypocalcaemia on their own – instead, their effects on each other (e.g., magnesium and PTH resistance) coalesce to form the foundational pathogenesis.

Despite the proposition of chronic stress as a key player in tetanic aetiology, it is suggested that it may not be one of the salient factors. Stress and its responses, including anxiety, may not primarily induce hypocalcaemia and tetany – instead, their repercussions may prove to be exacerbating factors in the development of the condition. Frequent episodes involving bouts of anxiety may negatively impact renal or neurobiological processes, contributing to the physiological mechanisms that characterize hypocalcaemia.

It must be stated that the mechanistic links made between chronic stress to tetany are indirect – this arises from the paucity of information available in recent scientific literature. Research provided invaluable, and yet fragmentary, explanations for the possible neurological reverberations of stress response systems.

Nevertheless, the outlined mechanisms suffice to propose chronic stress as an important contributing factor to tetany. While these tetanic seizures and cramps remain less of an enigma today, further research in the field may allow a more fulfilling understanding of the condition, aiding both patients and physicians.

References

[1] N. Ito, S. Fukumoto, "Symptoms and management of tetany," *Clin. Calcium*, vol. 17, no. 8, pp. 1234–1239, Aug. 2007.

[2] J. Loscalzo, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo, J. L. Jameson, "Numbness, Tingling and Sensory Loss," in *Harrison's Principles of Internal Medicine,* 21st ed., vol. 1, New York, USA: McGraw-Hill, 2022, pp. 756–757.

[3] D. Ganten, K. Ruckpaul, *Encyclopedic Reference of Genomics and Proteomics in Molecular Medicine,* 1st ed., vol. 1, New York, USA: Springer-Verlag, 2006.

[4] A. Williams, D. Liddle, V. Abraham, "Tetany: A diagnostic dilemma," *J Anaesthiol Clin Pharmacol*, vol. 27, no. 3, pp. 393–394, Sep. 2011.

[5] J. E. Hall, M. E. Hall, "Membrane physiology, nerve, and muscle," in *Guyton and Hall Textbook of Medical Physiology*, 14th ed., vol. 1, Amsterdam, Netherlands: Elsevier, 2021, pp. 71–1014.

[6] J. G. Adams et al., "Calcium, magnesium and phosphorus," in *Emergency Medicine Clinical Essentials,* 2nd ed., vol. 1, Amsterdam, Netherlands: Elsevier, 2013, pp. 1405–1417.

[7] R. C. Tsang et al., "Possible pathogenetic factors in neonatal hypocalcemia of prematurity," *The Journal of Pediatrics,* vol. 82, no. 3, pp. 423–429, Mar. 1973.

[8] M. Sutters et al., "Severe hyperphosphatemia and hypocalcemia: a dilemma in patient management," *J Am Soc Nephrol.,* vol. 7, no. 10, pp. 2056–2061, Oct. 1996.

[9] B. Haldimann, K. Vogt, "Hyperphosphatemia and tetany following phosphate enema," *Schweiz Med Wochenschr.,* vol. 113, no. 35, pp. 1231–1233, Sep. 1983.

[10] P. Torres, "Three feedback loops precisely regulating serum phosphate concentration," *Kidney International,* vol. 80, no. 1, pp. 443–445, Sep. 2011.

[11] D. Bikle, "Vitamin D metabolism, mechanism of action, and clinical applications," *Chemistry & Biology*, vol. 21, no. 3, pp. 319–329, Mar. 2014.

[12] S. Fukumoto, "Phosphate metabolism and vitamin D," *Bonekey Rep.,* vol. 3, no. 1, pp. 497–498, Feb. 2014.

[13] M. Christov, H Jüppner, "Phosphate homeostasis disorders," *Best Pract Res Clin Endocrinol Metab.,* vol. 32, no. 5, pp. 685–706, Oct. 2018.

[14] J. Leung, M. Crook, "Disorders of phosphate metabolism," *J Clin Pathol.,* vol. 72, no. 11, pp. 741–747, Nov. 2019.

[15] M. Helikson, W. Parham, J. Tobias, "Hypocalcemia and Hyperphosphatemia After Phosphate Enema Use in a Child," *J Ped Surg.,* vol. 32, no. 8, pp. 1244–1246, Aug. 1997.

[16] J. Soar, G. Perkins, G. Abbas et al., "European Resuscitation Council Guidelines for Resuscitation 2 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution," *Resuscitation,* vol. 81, no. 10, pp. 1400–1433, Oct. 2010.

[17] R. Elin, "Magnesium metabolism in health and disease," *Dis Mon.,* vol. 34, no. 4, pp. 161–218, Apr. 1988.

[18] J. Hoenderop, S. Ferre, R. Bindels, "Sensing mechanisms involved in Ca2+ and Mg2+ homeostasis," *Kidney Int.,* vol. 82, no. 11, pp. 1157–1166, Dec. 2012.

[19] A. Khan, H. Al-Azem, "Hypoparathyroidism," *Best Pract Res Clin Endocrinol Metab.,* vol. 26, no. 4, pp. 517–522, Aug. 2012.

[20] R. Reilly, D. Ellison, "Mammalian distal tubule: physiology, pathophysiology, and molecular anatomy," *Physiol Rev.,* vol. 80, no. 1, pp. 277–313, Jan. 2000.

[21] B. Glaudemans et al., "New molecular players facilitating Mg(2+) reabsorption in the distal convoluted tubule," *Kidney Int.,* vol. 77, no. 1, pp. 17–22, Jan. 2010.

[22] H. Kesteloot, J. Joossens, "The relationship between dietary intake and urinary excretion of sodium, potassium, calcium and magnesium: Belgian Interuniversity Research on Nutrition and Health," *J Hum Hypertens.,* vol. 4, no. 5, pp. 527–533, Oct. 1990.

[23] J. Kopple, J. Coburn, "Metabolic studies of low protein diets in uremia. II. Calcium, phosphorus and magnesium," *Medicine (Baltimore),* vol. 52, no. 6, pp. 597–607, Nov. 1973.

[24] H. Spencer, M. Lesniak, C. Gatza et al., "Magnesium absorption and metabolism in patients with chronic renal failure and in patients with normal renal function," *Gastroenterology,* vol. 79, no. 1, pp. 26–34, Jul. 1980.

[25] A. Alfrey, N. Miller, R. Trow, "Effect of age and magnesium depletion on bone magnesium pools in rats," *J Clin Invest.,* vol. 54, no. 5, pp. 1074–1081, Nov. 1974.

[26] L. Kayne, D. Lee, "Intestinal magnesium absorption," *Miner Electrolyte Metab.,* vol. 19, no. 4, pp. 210, Jan. 1993.

[27] J. Baaij, J. Hoenderop, R. Bindels, "Regulation of magnesium balance: lessons learned from human genetic disease," *Clin Kidney J.,* vol. 5, no. 1, pp. 15–24, Feb. 2012.

[28] K. Fine et al., "Intestinal absorption of magnesium from food and supplements," *J Clin Invest.,* vol. 88, no. 2, pp. 396–402, Aug. 1991.

[29] J. H. F. Baaij, J. Hoenderop, R. Bindels, "Magnesium in Man: Implications for Health and Disease," *Physiol. Rev.,* vol. 95, no. 1, pp. 1–46, Jan. 2015.

[30] G. Quamme, "Recent developments in intestinal magnesium absorption," *Curr Opin Gastroenterol.*, vol. 24, no. 2, pp. 230–235, Mar. 2008.
[31] A. Schmulen et al., "Effect of 1,25-(OH)2D3 on jejunal absorption of magnesium in patients with chronic renal disease," *Am J Physiol.*, vol. 238, no. 4, pp. 349–352, Apr. 1980.
[32] J. Hou, A. Renigunta et al., "Claudin-16 and claudin-19 interaction is required for their assembly into tight junctions and for renal reabsorption of magnesium," *Proc Natl Acad Sci U S A.*, vol. 106, no. 36, pp. 15350–15355, Sep. 2009.
[33] M. Konrad, A. Gomes et al., "Claudin-16 and claudin-19 interact and form a cation-selective tight junction complex," *J Clin Invest.*, vol. 118, no. 2, pp. 619–628, Feb. 2008.
[34] T. Voets, B. Nilius et al., "TRPM6 forms the Mg2+ influx channel involved in intestinal and renal Mg2+ absorption," *J Biol Chem.*, vol. 279, no. 1, pp. 19–25, Jan. 2004.
[35] A. Ikari, C. Okude et al., "TRPM6 expression and cell proliferation are up-regulated by phosphorylation of ERK1/2 in renal epithelial cells," *Biochem Biophys Res Commun.*, vol. 369, no. 4, pp. 1129–1133, May 2008.
[36] C. Huang, E. Kuo, "Mechanism of hypokalemia in magnesium deficiency," *J Am Soc Nephrol.*, vol. 18, no. 10, pp. 2649–2652, Oct. 2007.
[37] C. Birmingham, S Gritzner et al., "Heart failure in anorexia nervosa: case report and review of the literature," *Eat Weight Disord.*, vol. 12, no. 1, pp. 7–10, Mar. 2007.
[38] T. Nijenhuis, K. Renkema et al., "Acid-base status determines the renal expression of Ca2+ and Mg2+ transport proteins," *J Am Soc Nephrol.*, vol. 17, no. 3, pp. 617–626, Mar. 2006.
[39] S. Kurstjens, H. Bouras et al., "Determinants of hypomagnesemia in patients with type 2 diabetes mellitus," *Eur. J Endocrinol.*, vol. 176, no. 1, pp. 11–19, Jan. 2017.
[40] G. Quamme, "Renal handling of magnesium," in *Massry and Glassock's Textbook of Nephrology*, 4th ed., vol. 1, Baltimore, USA: Lippincott Williams & Wilkins, 2001, pp. 344–350.
[41] B. Mandon et al., "Insulin stimulates Na+, Cl-, Ca2+, and Mg2+ transports in TAL of mouse nephron: cross-potentiation with AVP," *Am J Physiol.*, vol. 265, no. 3, pp. 361–369, Sep. 1993.
[42] Z. Agus, "Hypomagnesemia," *J Am Soc Nephrol.*, vol. 10, no. 7, pp. 1616–1622, Jul. 1999.
[43] J. Freitag et al., "Skeletal resistance to parathyroid hormone in magnesium deficiency: Studies in isolated perfused bone," *J Clin Invest.*, vol. 64, no. 1, p. 1238–1244, Jan. 1979.
[44] A. Arabi et al., "Hypovitaminosis D in developing countries - prevalence, risk factors and outcomes," *Nat Rev Endocrinol.*, vol. 6, no. 1, pp. 550–561, Jan. 2010.
[45] P. Han, B. Trinidad et al., "Hypocalcemia-Induced Seizure: Demystifying the Calcium Paradox," *ASN Neuro.*, vol. 7, no. 2, Apr. 2015.
[46] T. Wang et al., "Small physiologic changes in calcium and magnesium alter excitability and burst firing of CA1 pyramidal cells in rat hippocampal slices," *J Neurosurg Anesthesiol.*, vol. 16, no. 3, pp. 201–209, Jul. 2004.
[47] P. Gilon et al., "NALCN: a regulated leak channel," *EMBO Rep.*, vol. 10, no. 9, pp. 963–964, Sep. 2009.
[48] B. Lu et al., "Extracellular Calcium Controls Background Current and Neuronal Excitability via an UNC79-UNC80-NALCN Cation Channel Complex," *Neuron.*, vol. 68, no. 3, pp. 488–499, Nov. 2010.
[49] P. Sah, "Ca(2+)-activated K+ currents in neurones: types, physiological roles and modulation," *Trends Neurosci.*, vol. 19, no. 4, pp. 150–154, Apr. 1996.
[50] C. Conway et al., "Chronic environmental stress and the temporal course of depression and panic disorder: a trait-state-occasion modeling approach," *J Abnormal Psychol.*, vol. 125, no. 1, pp. 53–63, Jan. 2016.
[51] C. Song et al., "Chronic stress impairs GABAergic control of amygdala through suppressing the tonic GABAA receptor currents," *Mol. Brain.*, vol. 24, no. 7, pp. 32, Apr. 2014.
[52] S. Masneuf et al., "Glutamatergic mechanisms associated with stress-induced amygdala excitability and anxiety-related behavior," *Neuropharmacol.*, vol. 85, no. 1, pp. 190–197, Oct. 2014.
[53] A. Goddard, "The Neurobiology of Panic: A Chronic Stress Disorder," *Chronic Stress (Thousand Oaks)*, vol. 1, no. 1, pp. 1, Jan. 2017.
[54] R. Krapf et al., "Chronic respiratory alkalosis induces renal PTH-resistance, hyperphosphatemia and hypocalcemia in humans," *Kidney Int.*, vol. 42, no. 3, pp. 727–734, Sep. 1992.
[55] M. Binker et al., "Acute pancreatitis: The stress factor," *World J Gastroenterol.*, vol. 20, no. 19, pp. 5801–5807, May 2014.
[56] K. Han et al., "Stress and Sleep Disorder," *Exp Neurobiol.*, vol. 21, no. 4, pp. 141–150, Dec. 2012.
[57] Y. Ilan et al., "Prolonged sleep-deprivation induced disturbed liver functions serum lipid levels, and hyperphosphatemia," *Eur. J Clin. Invest.*, vol. 22, no. 11, pp. 740–743, Nov. 1992.