Biochemical functions of magnesium

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Summary

Magnesium is required by many enzymes as a co-factor and may couple primarily with the enzyme or the substrate in different reactions.

Free cytosolic magnesium affects cell energy, the action of various hormones on target cells, protein synthesis and cellular electrolyte content.

Magnesium enters the cell by a process of facilitated diffusion requiring a transporter, and leaves it by an active process utilizing adenosine triphosphate.

S Afr Med J 1983; **63**: 353-355.

Magnesium (Mg^{2+}) is one of several biochemically important metallic ions which act as co-factors to fundamental enzyme reactions in man. Combinations formed between metallic ions and enzymes or their substrates may influence both the equilibrium and velocity of enzymatic reactions, sometimes with significant metabolic consequences.

Two processes are frequently encountered when the effect of a metallic ion upon the velocity of an enzymatic reaction is considered. In some cases, a metallic ion (M) may combine with an enzyme (E). The combination thus formed (ME) has an active conformation and combines with the substrate (S); the complex thus formed (MES) yields the final products of the reaction:

$$E + M = ME$$
$$ME + S = MES$$
$$MES \rightarrow ME + \text{products} \quad \ldots\ldots\ldots\ldots \text{(A)}.$$

Alternatively, a metallic ion may combine with the substrate and not with the enzyme, in which case the true substrate of the reaction is the complex (MS) formed by the substrate and the metallic ion:

$$M + S = MS$$
$$MS + E = EMS$$
$$EMS \rightarrow E + M + \text{products} \quad \ldots\ldots\ldots\ldots \text{(B)}.$$

Magnesium ions may affect enzyme kinetics through either of these two models. A typical example of the first reaction (A) is provided by the action of magnesium upon the enolase that catalyses the dehydration of 2-phosphoglyceric acid to phosphoenolpyruvate during glycolysis.[1] The enzyme consists of two subunits and is activated by uniting with two magnesium ions:

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Date received: 13 October 1982.

$$E + 2M = M_2E$$
$$M_2E + S = M_2ES \text{ (partial activity)}.$$

Activity is further increased by the combination of two more magnesium ions with the enzyme-substrate complex:

$$M_2ES + 2M = M_2ESM_2 \text{ (maximum activity)}.$$

The second type of reaction (B) is principally associated with the kinases which transfer a specific chemical group (Y) from a substrate (X) to another substrate (Z):

$$XY + Z \xrightarrow{\text{transferase}} X + ZY.$$

An example is provided by the transfer of phosphate from adenosine triphosphate (ATP) to another substrate, glucose, during glycolysis:

$$\text{ATP} + \text{glucose} = \text{ADP} + \text{glucose-6-phosphate}.$$

In this reaction, catalysed by hexokinase,[2] ATP is not the true substrate since magnesium must first form a chelate with the ß- and γ-phosphates of ATP before the reaction can proceed. Consequently, the reaction should be represented as follows:

$$Mg^{2+} + ATP^{4-} = Mg\text{-}ATP^{2-}$$
$$Mg\text{-}ATP^{2-} + \text{glucose} + E = Mg\text{-}ATP\text{-glucose } E$$
$$Mg\text{-}ATP\text{-glucose } E \rightarrow \text{glucose-6-phosphate} + Mg\text{-}ADP.$$

Magnesium ion, cellular energy level, and hormone actions

Magnesium concentration profoundly influences numerous metabolic pathways in man, consequently affecting intracellular energy levels, the action of hormones upon target cells and the functional integrity of cell membranes.

Intracellular ATP levels

Many metabolic reactions are regulated by the energy supply available within the cell at a given moment. The concept of 'energy charge' has been used to quantify this fact. This index relates the amount of high-energy bonds available to the total supply of nucleotides:

$$\text{Energy charge} = \frac{(\text{ATP}) + 1/2\,(\text{ADP})}{(\text{ATP}) + (\text{ADP}) + (\text{AMP})}.$$

The index may assume values from 0 (only adenosine monophosphate (AMP) exists) to 1 (only ATP exists); usually it falls within a narrow range which varies from 0,80 to 0,95 in different cell types. This value results from a balance between the processes that expend ATP (anabolism) and those which produce it (catabolism). Magnesium concentration is of critical importance to these reactions because the true substrate, whether ATP is produced or consumed, is a chelate with magnesium. When magnesium is depleted the velocities of these important enzymatic reactions are therefore reduced.

Production of cyclic adenosine monophosphate (cAMP)

Various water-soluble hormones such as calcitonin, catecholamines, glucagon, parathyroid hormone and vasopressin exert their actions on target cells in an indirect manner. These hormones cannot traverse the lipid-containing cell membrane because they are water-soluble and therefore unite with a molecule on the outer surface of the cell membrane. This sets in motion a series of processes including the activation of adenylate cyclase and ending with the intracellular production of cAMP in a concentration directly proportional to the amount of hormone bound to the receptor.

cAMP activates one or more kinases which, in turn, catalyse diverse metabolic processes affecting the energy level within the cell.

Composition of the adenylate cyclase system

Adenylate cyclase forms part of the inner surface of the cell membrane where it usually exists in an inactive form. The conformation of this pro-enzyme is changed by a series of specific activators,

$$\text{Mg-ATP}^{2-} \xrightarrow[\text{(active)}]{\text{adenylate cyclase}} \text{cAMP} + \text{Mg}^{2+} + \text{PPi} + \text{H}^{+},$$

where PPi represents inorganic pyrophosphate. The cAMP formed is hydrolysed in due course by an intracellular phosphodiesterase, which also requires magnesium as a co-factor:

$$\text{cAMP} + \text{H}_2\text{O} \xrightarrow[\text{Mg}^{2+}]{\text{phosphodiesterase}} \text{AMP} + \text{H}^{+}.$$

A set of proteins in the outer surface of cell membranes are capable of specifically recognizing any signal reaching the target cell. These proteins, which are receptors by definition, sometimes occupy the entire thickness of the cell membrane. Once a hormone-receptor complex has been formed a poorly understood series of reactions begins, leading to the activation of adenylate cyclase. Three possible mediators exist between the reception of the signal, whether it be of hormonal or other origin, and the activation of adenylate cyclase. These include some prostaglandins and two proteins designated G/F protein and calmodulin respectively.

Prostaglandins are soluble in cell membranes because of their lipid structure, and some may activate adenylate cyclase. Others reaching the interior of the cell activate phosphodiesterase.

G/F protein[3] is encountered at the inner surface of the cell membrane in an inactive form which is activated in the presence of magnesium and guanosine triphosphate (GTP) once a hormone-receptor complex has formed at the cell membrane. Magnesium activates the G/F protein directly and is also required to form the chelate with ATP which is the true substrate of the adenylate cyclase system. GTP has important activating and retarding functions. G/F protein acts as a GTPase, catalysing the following reaction at a very low velocity:

$$\text{GTP} + \text{H}_2\text{O} = \text{GDP} + \text{Pi},$$

where Pi is inorganic phosphate. G/F protein is inactivated when this reaction occurs and the adenylate cyclase system is retarded in consequence. Conversion of guanosine diphosphate (GDP) to GTP is necessary for its reactivation.

Calmodulin, a polypeptide found in animal and plant cells, is a calcium-dependent regulator which acts as a membrane and intracellular receptor for calcium ions.[4] Calcium concentration is higher in the extracellular fluid than in the cytosol and the cell membrane is normally impermeable to the ion. Calcium flows across the cell membrane when the latter becomes temporarily permeable in response to an electrical impulse or other signal. The change in the transmembrane calcium gradient provoked then activates adenylate cyclase *per se*. Calcium ions which enter the cell bind to calmodulin at carboxylate groups, activating the polypeptide in the process. Activated cytosolic calmodulin influences various biochemical reactions. It unites to adenylate cyclase and activates it in turn, thus stimulating the formation of cAMP. Increased activity of phosphodiesterase may also occur with consequent breakdown of cAMP, and reactions involving the synthesis of neurotransmitters, glycogen metabolism, and contraction of myosin are also regulated.

The passage of calcium from cytosol to the exterior of the cell is mediated by Ca^{2+}-ATPase, an enzyme that hydrolyses Mg-ATP^{2-}, while calcium is being transported. The action of Ca^{2+}-ATPase is modulated by active calmodulin. If the intracellular concentration of active calmodulin rises too steeply the activity of the enzyme increases, and passage of calcium from the cell is promoted. Diminution in the cellular concentration of magnesium causes a loss in activity of Ca^{2+}-ATPase, resulting in a further rise in intracellular concentration.

Effects of the magnesium ion on protein synthesis

Protein synthesis is a complex process which takes place within the ribosomes and requires a series of molecules that are synthesized elsewhere in the cell. Magnesium ions are required for the process of protein synthesis itself and for the conformation of various molecules related to it,[5] and are indispensable to the processes involved in RNA synthesis.[5] Mg-ATP^{2-} is essential in the binding of amino acids to transfer RNA and also for stabilizing the structure of the resulting complex. The ribosome divides into two subunits once the biosynthetic process has begun. An adequate local concentration of magnesium, within narrow limits, is necessary for the initiation of protein biosynthesis and for maintaining the functional integrity of the unified ribosome and the ribosomal subunits.

Effects of the magnesium ion upon cellular electrolyte composition

Magnesium is a co-factor for the Na^{+}, K^{+}-ATPase which catalyses active passage of sodium from the cell and entrance of potassium into the cell (sodium/potassium pump).[6-8] It is also a co-factor of Ca^{2+}-ATPase which catalyses the active transport of calcium ions from the cytosol to the endoplasmic reticulum.

Cellular transport of magnesium

Studies utilizing magnesium isotopes[3,5] have shown that the passage of the ion through the cell membrane requires a transporter that follows Michaelis-Menten kinetics. The transport system appears to be active and therefore to consume ATP. It has been postulated that the transport of magnesium across the cell membrane is mediated by a receptor which also activates the adenylate cyclase system; a protein transporter for magnesium may exist that forms part of the adenylate cyclase system but produces cAMP when it transports magnesium.[9]

Within the cell exchanges across mitochondrial membranes also exist. In the presence of phosphate ions myocardial mitochondria accumulate large amounts of magnesium ions and liberate hydrogen ions. Liver mitochondria lose magnesium when they accumulate calcium. Both processes are mediated by a transporter that follows Michaelis-Menten kinetics.

Thermodynamic calculations that take into account the relative concentrations of magnesium within and outside the mitochondria and the cell lead to the conclusion that the entrance of magnesium into the cell occurs through facilitated diffusion requiring a transporter, whereas the exit of magnesium from the cell is an active transport process which expends ATP.

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The Black heart in southern Africa — a geographical view of the future

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Summary

The dearth of geographical analyses of heart conditions among the Blacks of southern Africa is contrasted with the well-defined patterns in several countries. By analogy with studies of cancer among Blacks it is argued that similar-order spatial variations of heart-related morbidity are likely to exist, and that knowledge of them is essential in planning services for a health problem of growing urgency.

S Afr Med J 1983; **63:** 355-359.

The idea that man's environment plays a major role in influencing human health dates back to classical times. In spite of Hippocrates' directive to his students over 2 000 years ago, 'first study the place',[1] those who have followed in his profession have paid only lip-service to his original emphasis on man as a creature of his environmental setting. Some of the reason stems from medicine's traditional concern with the clinical individual, often examined in isolation from his own daily environmental hazards and surroundings. Thus the concept of the collective health of communities is a new-found but rational trend back toward the Hippocratic instruction.

A second reason for 2 000 years' disregard of environmental influence has to do with the availability of quantitative data, not only about geographical factors but also with regard to assemblies of information about ill-health. Only over the last century have mortality data gradually been greatly improved by the development, now through nine revisions, of the International Classification of Disease (ICD). Initially applying only to France and then to Europe, this code now permits standardized diagnosis, nomenclature and recording of deaths on an international basis.[2] Although it has imperfections, basically those of human operators of the code, the use of the ICD now permits, for most fatal illnesses, a reasonable geographical basis of comparison across the world, either at inter- or at intranational level.

Similarly, many factors of our surroundings, especially the physical parameters, can now be measured. Such items as precipitation, relative humidity and soil chemistry are eminently quantifiable and so can be correlated with ill-health. Less measurable, even today, are human factors like tobacco, alcohol consumption, nutritive intake or stress. That is not to say, however, that these should be ignored but merely that we must be prepared to seek surrogate measures of relevance to each problem. For example, traffic density and rate of increase may provide suitable surrogates for physical insults to human hearing in urban areas, where noise levels are said to be on the increase at a rate of doubling each decade.

Difficult to measure too is the whole gamut of changes of lifestyle, known collectively as 'culture shock'. Consider the Black man uprooted — for economic reasons — from his village on the banks of Kipling's great grey-green greasy Limpopo river to work on the gold mines of Welkom or at Iscor or Cape Explosives. No doubt his heart will pine for the maidens left behind him but, of greater medical interest, his heart will be subjected to a variety of unaccustomed insults, particularly diet- and stress-related ones. The implications of wholesale mobility in today's world, whether as part of the guest-worker phenomenon or as holiday tourists or as daily commuters through city traffic, have not been sufficiently recognized as involving major inputs of stress. Another unquantified source of stress in today's world economic climate relates to the malaise of either actual or potential retrenchment from employment, hanging as a spectre

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Paper presented at the Symposium on Cardiology in a Tropical Environment, Durban, 1 - 3 September 1982.