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Prace przeglądowe

S.A. Kiss[1], Z. Galbács[2], G. Galbács[2]

THE ROLE OF MAGNESIUM IN THE SUPPOSED MECHANISM OF ANAESTHESIA

[1]Hungarian Magnesium Society, Szeged, Fő fasor 73A/2
[2]University of Szeged, Dept. of Inorg. and Anal. Chem., Szeged, Dóm tér 7

INTRODUCTION

The anaesthetic, narcotic effect of magnesium has been discussed since the work of MELTZER-AUGER (1906), but its mechanism has not been clarified yet. MANSFELD-BOSÁNYI (1913) tried to explain the narcotic effect by performing gravimetric experiments. Their investigations showed that the magnesium content of a cat's brain did not change upon the use of either chloroform or magnesium for anaesthesia. Therefore, they assumed that Mg did not penetrate into the cell, but stuck in the „plasma-skin" („plasmahaut", now called membrane) and imposed its effect there. By making this assumption they made progress in the knowledge of their time, as the double lipid layer of membranes was discovered by GARTER-GENDER only in 1925.

dr. Sándor A. Kiss, President of the Hungarian Magnesium Society, 6726 Szeged, Fő fasor 73A/2, Hungary. Tel./fax: 36-62-432-298, e-mail: sakiss@freemail.hu

ANESTHETIC EFFECT OF MAGNESIUM

SINCE 1906, numerous publications have appeared on the effect of Mg on the central nervous system. Without attempting to fully cover this range of publications, we shall cite here only some of the recent articles.

BAC et al. (1996) report on the increase of pain sensitivity by Mg-deficiency. According to the studies of DUBRAY et al. (1996), the pain level of rats on clamping their legs could be decreased by Mg dosing. ATTYGALLE-RODRIGO (1997) described the spasm hindering impact of Mg infusion. The serum Mg content increased from the 0.8–1.1 $mM \cdot dm^{-3}$ normal value to 2–4 $mM \cdot dm^{-3}$ during the therapy, but 6 $mM \cdot dm^{-3}$ Mg level was needed for areflexia. The finding of RAMATHYN et al. (1988) is also worth mentioning, according to which an increase of Mg/Ca ratio (hypocalcemia) correlates better with the „anaesthetic" effect than serum Mg levels.

COUNTINHO (1966) explains the „anaesthetic" effect of magnesium by the hindering of Ca transport. His experiments were performed on synthetic membranes and he could not describe the mechanism adequately either. DICHT-VIERLING (1991) studied the impact of magnesium concentration on the Ca ion flow of cardiac muscle (Figure 1). According to JAMES (1992) magnesium hinders the calcium caused release of transmitters (acetylcholine) from the vesicles, and that is why they have sedative effect.

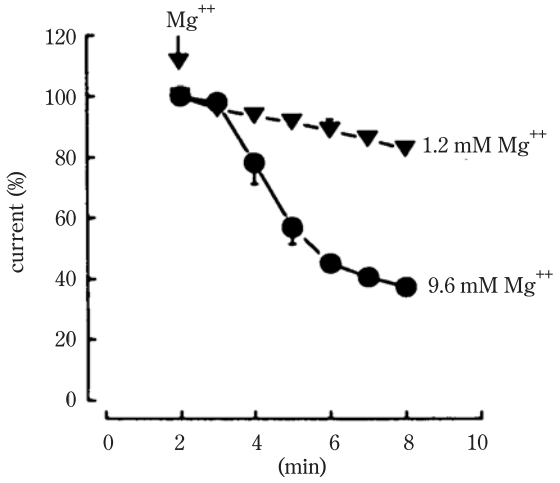

Fig. 1. Slow inward current at different magnesium concentrations
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ORGANIC ANAESTHETICS AND PHOSPHOLIPIDS

FEINSTEIN (1964) explains the effect of different local organic anaesthetic compounds, suggesting that they inhibit the Ca transport through the membrane. He concluded this from the finding that both rat muscle microsoma extracts and artificial membranes (lipid impregnated Millipore filters) showed resistance increase upon treatment with tetracaine (Figure 2). At the same time, sodium dosing was not found to decrease resistance. FEINSTEIN (1964) also observed that the pH of the phospholipid sol decreased from 6 to 5 when tetracaine was applied. NaCl had no effect on its pH (Figure 3).

Different local organic anaesthetic compounds (tetracaine, butacaine, procaine) coagulate phospholipids depending on their concentration; this was evidenced by the turbidity increase in Feinstein's experiments (Figure 4). This change means that the fluidity of membranes decreases and their rigidity increases.

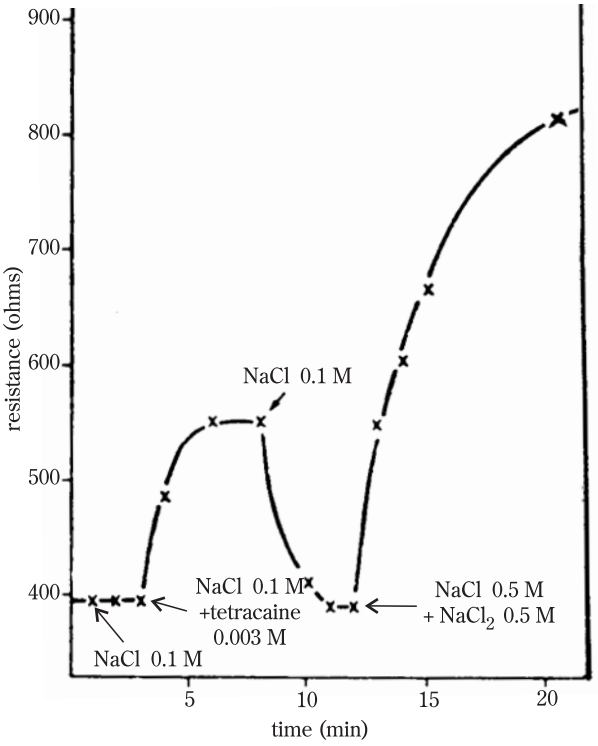

Fig. 2. The effects of Na^+, K^+, Ca^{2+}, and tetracaine HCl on the resistance of Millipore filter membranes impregnated with cephalin plus chloresterol

FEINSTEIN M.B. 1964. *Reaction of local anesthetics with phospholipids*. J. Gen. Physiol., 48: 57-374. Reproduced from the J. of General Physiology by copyright permission of the Rockefeller University Press.

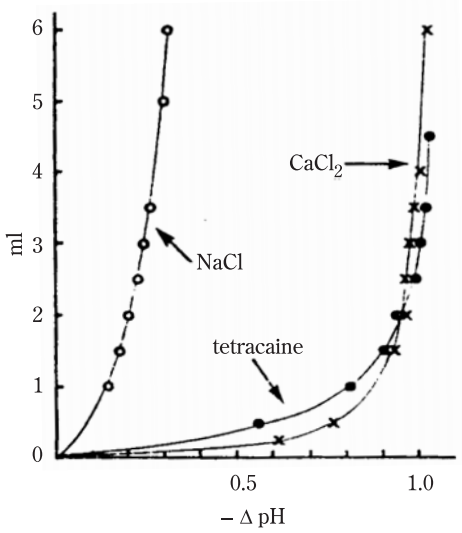

Fig. 3. Titration of 30 ml aliquots of a cephalin dispersion in water by 0.05 M solution of NaCl, $CaCl_2$, and tetracaine HCl. All solutions were adjusted to pH 6.00±0.01 before titration. ΔpH indicates the fall in pH observed as the salts were added. Temperature 22 ŝC, atmosphere N_2

FEINSTEIN M.B. 1964. *Reaction of local anesthetics with phospholipids*, J. Gen. Physiol., 48: 357-374.Reproduced from the J. of General Physiology by copyright permission of the Rockefeller University Press.

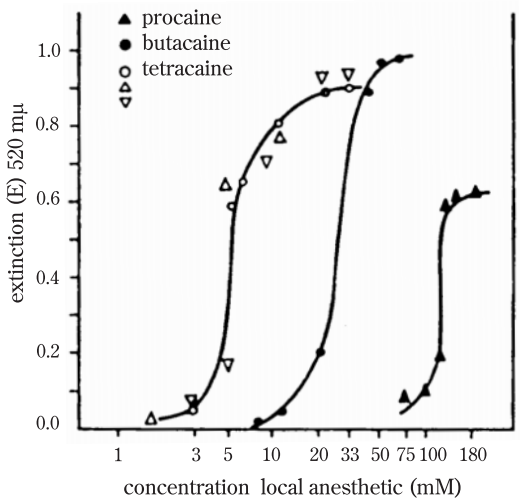

Fig. 4. The effect of local anaesthetics on the turbidity of aqueous dispersions of phospholipids. Tetracaine HCl was added to cephalin (o), phosphatidyl ethanolamine (Δ), and phosphatidyl serine (∇) dispersions. Butacaine sulfate (•) and procaine HCl (t) were added to cephalin dispersions.

FEINSTEIN M.B. 1964. *Reaction of local anesthetics with phospholopids*. J. Gen. Physiol, 48: 357-354.Reproduced from the J. of General Physiology by copyright permission of the Rockefeller University Press.

According to the theory of a local anaesthesia mechanism set up by FEINSTEIN (1964) – Figure 5, anaesthesia occurs when two phospholipid molecules of the membrane bind to each other. The anaesthetic agent binds in through the phosphate group of the phospholipid molecules and an H^+ is released; this is the reason of the decrease of pH. The binding between the two lipid molecules inhibits their rotational, wandering and „flip-flop" movements, so the ion transport by the membrane ion channel („kink") and/or the carrier deceases, and anesthesia occurs.

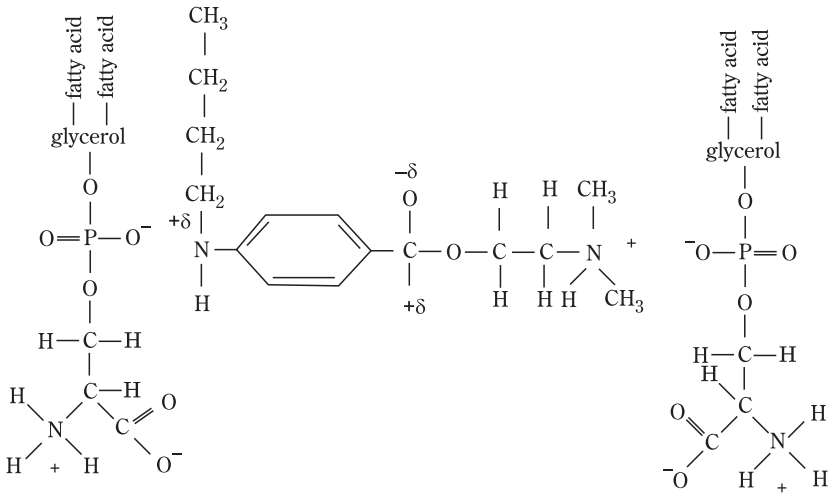

Fig. 5. Proposed model for the mechanism of complex formation between acidic phospholipids and local anaesthetics

FEINSSTEIN M.B. 1964. *Reaction of local anesthetics with phospholipids*. J. Gen. Physiol., 48: 357-374. Reproduced from the J. of General Physiology by copyright permission of the Rockefeller University Press.

MAGNESIUM AND THE PHOSPHOLIPIDS

Our vision of the mechanism of the Mg anaesthetic effect is similar to that proposed by FEINSTEIN (1964) – Figure 6. Magnesium reversibly binds to the phosphate groups of two phospholipid molecules, decreasing the fluidity of the membrane and permeability. However, calcium can also bind to phospholipids, but in this way it would be enriched due to a stronger bond, which in turn can cause the cell to decrease. If the binding of magnesium to phospholipids was not reversible, then the anaesthesia would not disappear after some time. This temporal

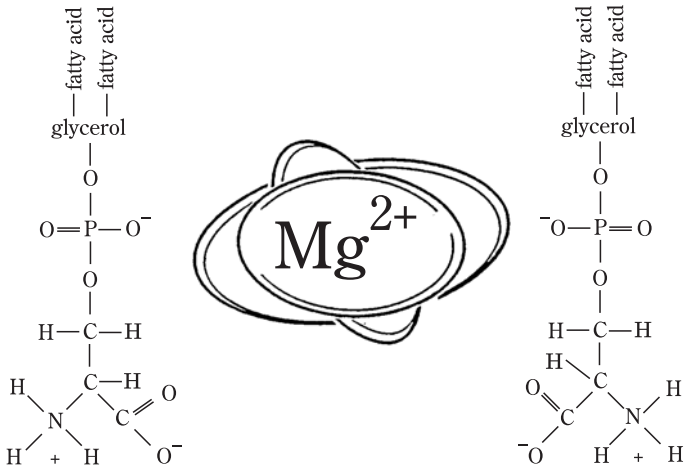

Fig. 6. Proposed model for the mechanism of complex formation between acidic phospholipids and local anaesthetics of magnesium (original)

effect can be seen on Figure 1, when the blocking of Ca decreases in time due to the „dilution" of magnesium.

The in vitro studies of RAYSSIGUIER et al. (1991) proved that membrane fluidity increased by 20-40% in the case of Mg deficiency. Concordant findings were also published by TONGYAI et al. (1989).

MAGNESIUM AND THE NEURO EXCITATION

Feeling of pain is based on excitatory neurotransmission. This is achieved by the acetylcholine transmitter between the pre- and postsynaptic terminals. In a relaxed status, acetylcholine can be found in vesicles. Vesicles are stabilized by magnesium, that is, magnesium prevents the opening of the membrane walls, thus acetylcholine cannot be released (Figure 7). Calcium ions can bind more strongly to the membrane than magnesium, therefore Ca can extrude Mg if present in sufficiently high concentration. This can cause the membrane to open and neuroexcitatory transmission can occur. A consequence of this is the inhibiting effect of calcium on anaesthesia. In a relaxed cell status, the Ca concentration is very low (10^{-6} mol·dm^{-3}), so the stabilisation of Mg (10^{-3} mol·dm^{-3}) can come to effect (BALLA-KISS 1996). If the Mg concentration is increased by intravenous infusion, the effect of Ca cannot appear. The result of the increased Mg content is a decrease in the Ca influx, which favours anaesthesia. According MITANI (1992), this can also be expressed in terms of the narrowing of the Ca ion channel and blocking of Ca input.

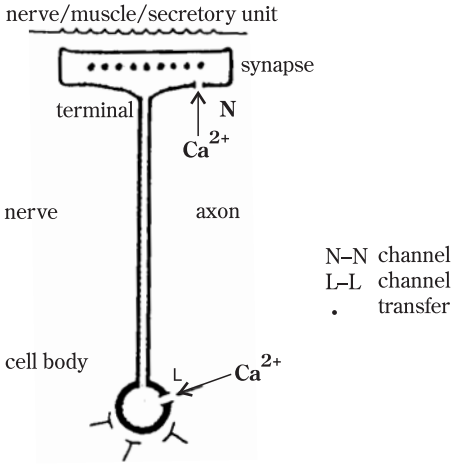

Fig.7. Schematic representation of the Ca^{2+} requirements of activation processes in nerve cells
MARIOTT J.F, WILLIAMS R.H. 1990. *Calcium antagonisms of action and novel indications*. Pharmaceutical J., 244: 266-269, with permission from the Editor.

RELATION BETWEEN ANAESTHESIA AND ATP

Since the work of DUBOIS et al. (1943) we have known that ATP concentration of muscles and brain increases in anaesthesia initiated by either magnesium or ether, due to the lower activity of ATP-ase. The reason for this can be found in the changed Ca/Mg ratio. The activity of ATP-ase is enhanced by Ca ions, while Mg ions inhibit it. The reduced activity of ATP-ase is therefore a consequence of such interaction of Ca and Mg ions. This reduced activity leads then to a decrease in the rate of ATP decomposition, thus energy transmission decreases too. As all biological „movements" (muscle contraction, neuroexcitatory transmission, etc.) require energy, so when the energy supply dissipates, anaesthesia occurs.

The antagonistic effect of Ca and Mg ions to the ATP-ase activity was evidenced in the experiment of DUBOIS (1943) by the fact that when Ca treatment was also applied in ether or magnesium anaesthesia of rats, the accumulation of ATP was not observed, that is the inhibition of ATP-ase decreased.

CALCIUM CHANNEL BLOCKERS

Four types of Ca ion channels are known to exist in membranes. These are the RCO (receptor operated ~) and VCO (voltage operated ~) channels, where

the latter can be broken up into three subtypes: L (long lasting), T (transient or short acting) and N (neuronal). Out of these, only RCO and L types are sensitive to conventional Ca antagonist medicines. In contrast, magnesium inhibits the Ca transport through all types of channels (Figure 8). The N type channel can be found in the presynaptic terminal of the neuron (MARIOTT-WILLIAMS 1990), therefore this is the place of the most direct inhibition by magnesium (Figure 7). Based on the above reasons it is possible to conclude that magnesium is a general anticonvulsant anesthetic.

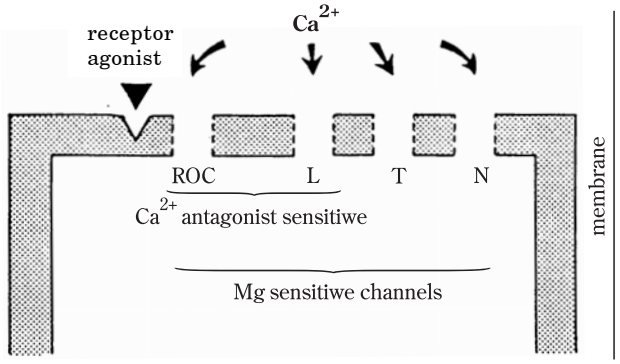

Fig. 8. Representation of the types of Ca^{2+} – channels involved in cellular activation. Receptor-operated channels (ROC) are activated by agonist-receptor combination and are partially sensitive to calcium antagonists. L (long lasting), T (transient) and N (neuronal) channels are activated by membrane depolarisation, though only L channels appear to sensitive to calcium antagonists

MARIOTT J.F., WILLIAMS R.H. 1990. *Calcium antagonism mechanisms of action and novel indications*. Pharmaceutical J., 244: 266-269, with permission from the Editor.

CONNECTION BETWEEN SERUM- AND CSF-MAGNESIUM

KIM et al. (1996) induced epileptic seizure by dosing lidocain intravenously. They observed that if the brain Mg level was increased by intra-cerebroventricular infusion then the lidocain threshold for seizure increased from 26 mg/body kg to 40 mg/body kg. By these in vivo rat experiments they proved the stimulus inhibiting effect of Mg. Intra-cerebroventricular infusion had to be used instead of intravenous one, because the Mg transport from blood to the brain was rendered almost impossible by the brain-blood-barrier (Figure 9). This is well reflected by HALLAK'S (1998) equation describing the connection between CSF (cerebrospinal fluid) and serum Mg:

$$Mg_{CSF} = 2.2657 + 0.054\ Mg_{serum}$$

where Mg_{serum} concentration is in $mg \cdot dl^{-1}dl$ units.

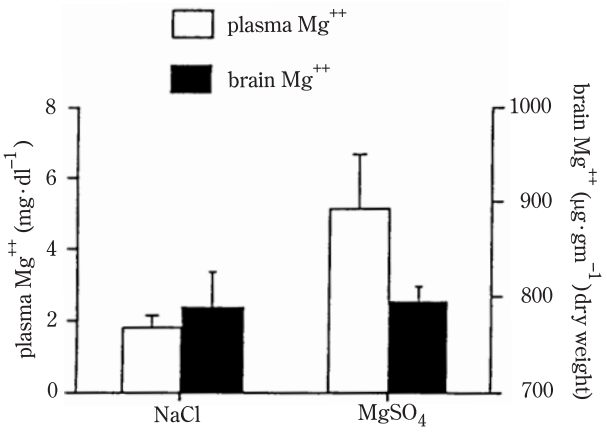

Fig. 9. Plasma and brain magnesium ion concentration after 5 days of continuous intravenous infusion of 0.9% NaCl or 50% $MgSO_4$. Despite an approximate threefold increase in plasma [Mg^{2+}], brain [Mg^{2+}] was unchanged

KIM Y.J., MCFARLANE C., WARNER D.S., BAKER M.T., CHOI W.W., DEXTER F. 1996. *The effect of plasma and brain magnesium concentrations on lidocaine-induced seizures in the rat*. Anasth. Analg., 83: 1223-12.

OPPELT et al. (1963) found that if the Mg content of serum in dogs was increased by 400% (after a 5 hour infusion), the Mg concentration in the cerebrospinal fluid (CSF) increased by max. 21%.

Also according to GHONEIM et al. (1970), magnesium enhances the efficiency of neuromuscular blocking agents, that is full anaesthesia can be achieved at a smaller concentration.

Experiments of BREYER-KANIG (1970) showed that Mg level of CSF in healthy (2.41 $mEqu \cdot dm^{-3}$) and ill patients (epileptic seizure, cerebral tumour, meningitis, cerebrovascular disease, etc.) differed by 2-6% on average, but the extreme values overlapped, so the difference was not significant. They concluded that even a small (some %) change in the magnesium concentration of CSF resulted in serious neurological consequences. It appears, however, that this „slight" change in Mg concentration is big enough to stop preeclampsia spasms (THURNAU et al. 1987). This may explain why MANSFELD-BOSÁNYI (1913) and later neurologists found no Mg level increase in the brain upon anaesthesia or narcosis.

EFFECT OF MAGNESIUM ON NMDA RECEPTORS

Magnesium can initiate anaesthesia through the inhibition of ion flow not only by its incorporation into the ion channel (phospholipids). Another pathway to block the ion channel is the inhibition of N-methyl-D-aspartate (NMDA) receptor which

opens the ion channel (HALLAK 1996). This can be achieved by hindering the binding of activating agents (e.g. glutamate, glycine, kainate) to the NMDA receptor. In addition to this, it helps the binding of inhibiting agents (e.g. MK-801). This is the reason why magnesium sulphate increases significantly (by 34%) the electronic excitatory threshold of the hippocampus, which causes neuro seizures (HALLAK 1992). It is to be noted, however, that the inhibition to excitatory neurons can be different in neurons of different locations even at the same Mg concentration.

CONCLUSION

Based on the above findings covering a wide range of research, we can explain the anaesthetic effect of Mg by the binding of magnesium to phospholipids and the consequent fluidity and permeability decrease of the membrane. This, at the same time, gives an explanation to the observed impact of Mg on the ion permeability of membranes too. Besides, it also blocks NMDA receptor, which is responsible for opening the ion channel; and this again leads to anaesthesia.

It can be stated, therefore, that the early theory of MANSFELD-BOSÁNYI (1913) for the mechanism of anaesthetic effect of magnesium, in which they reasoned the effect by the binding of Mg to the membrane („plasmahaut"), gained justification.

Acknowledgement

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THE ROLE OF MAGNESIUM IN THE SUPPOSED MECHANISM OF ANAESTHESIA

Keywords: anaesthesia, fluidity, ion transport, magnesium, membrane.

Abstract

The anaesthetic, narcotic effect of magnesium has been discussed since the publication of MELTZER-AUGER (1906), but its mechanism has not been clarified. Since then, other investigations have also been performed, but none of the publications has explained the issue. We propose a mechanism analogous to the studies made by FEINSTEIN (1964), who examined organic compounds showing anaesthetic effects. Our view is that magnesium abridges two phospholipids of the opposite sides of the membrane through their phosphate groups. This binding results in membrane rigidity, which makes the ion permeability provided by the ion channel and/or carrier decrease or discontinue, thus the halting of the Na^+, K^+ and Ca^{2+} ion flow eventually causes an anaesthetic effect. Another possible pathway is that magnesium ions block the activity of N-methyl-D-aspartate (NMDA) receptor to control the ion channel, which also lowers the permeability of the membrane.