Morphine and ethanol influence on magnesium concentration in serum and tissues of intoxicated mice

K. Pasternak[1], A. Papierkowski[2]

Summary

The effect of 5-day morphine and/or ethanol administration on total Mg content in blood serum, brain, heart, lung, kidney, liver, muscle and spleen in mice was studied. Significant hypomagnesemia was observed in all instances. Morphine caused the evident decrease of Mg content in brain, lung and kidney and increased Mg content in heart and spleen. Ethanol administration was associated with lower Mg content in brain and kidney, while it was elevated in liver, muscle and spleen. The probable causes and implications of the altered Mg tissue distribution are discussed.

Zusammenfassung

Der Einfluß einer 5-tägigen Verabreichung von Morphin und Ethanol auf die Serumkonzentration und den Gesamtmagnesiumgehalt in den Geweben der Mäuse wurde untersucht. Alle Tiere hatten eine Hypomagnesämie. Bei den mit Morphin behandelten Mäusen nahm der Gehirn-, Lungen- und Nieren-Magnesiumgehalt signifikant ab, wobei er im Herz- und Milzgewebe anstieg. Bei den mit Ethanol behandelten Mäusen wurde eine signifikante Abnahme des Magnesiumgehalts im Gehirn- und Nierengewebe und eine evidente Erhöhung im Leber-, Milz- und Muskelgewebe festgestellt. Aufgrund der vorliegenden Resultate kann man annehmen, daß die Intoxikation mit Morphin oder Ethanol eine veränderte Verteilung von Magnesium in den Geweben zur Folge hat. Die vermutlichen Ursachen dieser Tatsache werden diskutiert.

Introduction

Magnesium is the second most abundant intracellular cation in the human organism, second only to potassium. As the cofactor of over 300 enzymes Mg participates in several biochemical pathways, particulary in those involving the formation and utilisation of ATP. Many pathological symptoms and states can be in part attributed to altered Mg homeostasis [9–11]. Some clinical manifestation, although mostly non-specific, often involve neuromuscular, cardiovascular and psychiatric disturbances [5]. The symptoms seen in morphine or alcohol intoxication can sometimes resemble those of Mg depletion. It is well known that narcotics and ethanol exert various effects on animal and human organisms including the altered blood and tissue content of certain bioelements. These drugs are often consumed together by addicts in order to potentiale their effects.

The serum and intracellular levels of Mg are not always correlated and their concentrations can be independent. It is generally agreed that intracellular Mg concentration better reflects body stores than the serum level [9, 11].

Taking this into account we decided to estimate the eventual influences of morphine and ethanol on the serum and tissue content of Mg in mice.

Material and Methods

The investigations were performed on 40 male and female adult albino Swiss mice weighing 25–30 g, kept in cages at ambient temperature of 20–22°C on a natural day-night cycle. The animals had free access to standard laboratory food and were watered ad libitum. The Mg contents in the laboratory feed utilized (LSM feed) was 0.183% and the concentration of Mg in the drinking water was 19.98 mg per liter. The mice were divided into 4 groups consisting of 10 animals. Each group underwent the 5-day experimental regimen as follows:

Group I: Morphine was given intraperitoneally twice daily according to the following schedule: 1. day – 2 × 15 mg/kg, 2. day – 2 × 30 mg/kg, 3. day – 2 × 45 mg/kg, 4. day – 2 × 50 mg/kg and 5. day – 2 × 60 mg/kg [3].

Group II: The mice were treated with ethanol through a gastric tube once daily. The ethanol was given as a 20% solution in a dose of 2 g/kg body weight.

Group III: Morphine and ethanol were administered together according to the schedule used in groups I and II.

Group IV: served as a control. The animals received daily equivalent amounts of saline. During the period of the experiment no mice expired (mortality = 0).

On day six the mice were decapitated. The blood for Mg estimation was drawn from the heart and permitted coagulate in order to get the serum. The Mg content was also measured in brain, heart, lung, kidney, liver, femoral muscle and spleen tissues. The excised organs were weighed, washed with redestilled water, desiccated at 80°C for 72 h and incinerated at 450°C in a combustion furnace. The residues were dissolved in the spectrally pure HCl diluted with bidistilled water (1:1). The Mg was estimated by means of atomic absorption spectrophotometry (AAS) [4, 8]. The calibration was made using the model solutions of magnesium chloride. Mg concentration of serum was measured in μmol/L and its tissue content – in μg/g. Data are expressed as mean values ± SEM. Differences between treated mice and controls

[1] Department of Physiological Chemistry, Medical Academy of Lublin, Poland.
[2] Observation Clinic, Medical Academy of Lublin, Poland.

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Tab. 1: Blood serum (μmol/L) and tissue (μg/g) content of Mg in mice receiving morphine and ethanol.

Group	Serum	Brain	Heart	Lung	Kidney	Liver	Muscle	Spleen
I Morphine	201 ± 45**	8.3 ± 1.8	16.5 ± 2.9*	9.5 ± 1.5**	10.9 ± 0.8**	16.4 ± 2.6	13 ± 2.5	20.5 ± 3.7*
II Ethanol	164 ± 37***	7.6 ± 1.9*	14.4 ± 2.5	10.6 ± 0.8	11.3 ± 0.9*	19.1 ± 3.1*	14.7 ± 2.6*	19.3 ± 2.0*
III Morphine + Ethanol	214 ± 57**	6.4 ± 1.5**	16.8 ± 2.4*	8.6 ± 0.7***	11.0 ± 0.8**	16.8 ± 1.4	11.9 ± 1.8	17.1 ± 2.9
IV Control	271 ± 33	9.5 ± 2.3	14.4 ± 3.1	11.9 ± 1.6	12.4 ± 1.3	16.0 ± 2.4	12.3 ± 1.9	16.7 ± 3.4

Significant differences in comparison to control: * – $p < 0.05$; ** – $p < 0.01$; *** – $p < 0.001$.

were estimated by Student's t-test or Cochran-Cox's test. A p value < 0.05 was considered as significant.

Results

The basic effect caused by morphine and/or ethanol was a decrease in the concentration of Mg in most of the tested tissues in the experimental animals. This may have either been the result of a decrease in food consumption by intoxicated animals or the substances may have caused an increase in Mg utilization and/or an increase in its excretion.

As can be seen in table 1, the mean values of Mg concentrations of serum were significantly lower in groups I, II and III in comparison with controls. The statistical analysis revealed that the tissue content of Mg was significantly decreased in kidney (groups I, II and III), in brain (groups II and III) and in lung (groups I and III). Distinctly elevated amounts were seen in liver and muscle (group II) and in the spleen (groups I and II). There were no gross differences with regard to heart Mg content between mice given morphine or ethanol and control animals.

Changes in Mg concentration varies in different tissues. The increase in Mg concentration in the heart tissues of animals receiving morphine as a result of the passage of Mg caused changes in heart excitability.

Discussion

Though Mg is known to have a key role in various cellular functions, (which can be altered by morphine and ethanol), few studies have been performed to assess the influence of these drugs on Mg distribution in body fluids and tissues.

The results of our investigation show that the 5-day regimen of morphine and ethanol administration induced the significant decrease in total Mg concentration in blood serum and induced changes of Mg content in some tissues. It was previously stated that ethanol intoxication can lead to hypomagnesemia and hypermagnesuria in humans [2, 9, 10, 12]. *Petroianu* et al. [7] observed an inversely related diminution of Mg concentration with increasing serum ethanol levels during acute intoxication. The mechanism of hypomagnesemic effects of both morphine and alcohol remains unclear. It seems possible that they increase the urine excretion of Mg or may cause it's displacement from body fluids into some tissues. The increased tissue content in our experiments concerned the liver and muscle (after ethanol administration), and spleen (after morphine and ethanol). Recent studies have demonstrated that alcohol caused a decline in brain intracellular free Mg concentration in rats [6]. This would be in accordance with our results indicating the diminished total Mg brain content in mice treated with ethanol. It was observed that intracerebroventicularly injected $MgCl_2$ antagonized the analgesic effects of morphine in mice. There is considerable evidence that Ca and Mg are involved in the action of morphine, but the nature of this phenomenon remains obscure [1]. The most evident decrease of total Mg tissue content in our material was noted in the brain, lung and kidney after the administration of morphine or ethanol. The contemporaneous administration of these drugs seemed to potentiate this effect in the brain and lung tissue. The explanation of the described phenomena requires further studies including the determination of free Mg concentration in various body fluids and tissues.

In the light of our investigations one could postulate, that morphine and ethanol pose a hazard to Mg homeostasis in various organs in mice. If this is true also in humans, the Mg supplementation would be adivsable in drug addicts.

Conclusions

1. Morphine and ethanol as well as their combination cause hypomagnesemia and evident displacement of Mg in the tissues of tested mice.
2. Altered Mg tissue content under the influence of morphine, ethanol or both depends on the type of tissue.
3. Morphine and ethanol can be regarded as risk factors for Mg homeostasis.

References

[1] *Harris, R. A.; Loh, H. H.; Way, L.:* Effects of divalent cations, cation chelators and ionophore on morphine analgesia and tolerance. J. Pharm. Exp. Ther. **195** (1975) 488-498.

[2] *Laitinen, K.; Mamber-Allard, C.; Tunninen, R.; Karonen, S. L.; Tahtela, R.; Ylikahri, R.; Valimaki, M.:* Trancient hypoparathyroidism during acute alcohol intoxication. N. Engl. J. Med. **324** (1991) 721-727.

[3] *Männistö, P. T.; Borisenko, S. A.; Rauhala, P.; Toumainen, P.; Touminen, R. K.:* Variation in tolerance to the antinociceptive, hormonal and thermal effects of morphine after a 5-day pre-treatment of male rats with increasing doses of morphine. Naunyn Schmiedeberg's Arch. Pharmacol. **349** (1994) 161-169.

[4] *Marczenko, Z.:* Spektrofotometryczne oznaczanie pierwiastków. PWN, Warszawa 1974.

[5] *Millart, H.; Lamiable, D.; Collery, Ph.; Choisy, H.:* The determination of blood mononuclear magnesium content in normal subjects. Mg.-Bull. **10** (1988) 81–86.

[6] *Mullins, P. G. M.; Vink, R.:* Chronic alcohol exposure decreases brain intracellular free magnesium content in rats. Neurochemistry **6** (1995) 1633–1636.

[7] *Pertoianu, A.; Barquete, J.; Plentz, E. G.; Bastis, C.; Maia, D. Y.:* Acute effects of alcohol investigation on the human serum concentration of calcium and magnesium. J. Int. Med. Res. **19** (1991) 410–413.

[8] *Pinta, M.:* Absorbcynja spektrometria atomowa. PWN Warszawa 1974.

[9] *Reinhart, R. A.:* Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. Arch. Int. Med. **148** (1988) 2415–2420.

[10] *Rude, R. K.; Singer, F. R.:* Magnesium deficiency and excess. Ann. Rev. Med. **32** (1981) 245–259.

[11] *Truninger, B.; Banz, I.:* Magnesium and Phosphor – die vergessenen Elektrolyte. Schweiz. Med. Wschr. **113** (1983) 1602–1608.

[12] *Williamshemby, L.; Grant, K. A.; Gatto, G. J.; Porrino, L. J.:* Metabolic mapping of the effects of chronic voluntary ethanol consumption in rats. Pharmacol. Biochem. Behav. **54** (1996) 415–423.

Correspondence to:
Dr. med. *Kazimierz Pasternak,* Department of Physiological Chemistry, Medical Academy of Lublin, Lubartowska Street 85, 20-123 Lublin, Poland.