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注射硫酸镁并无中枢性抗惊厥作用[1]

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Parenteral magnesium sulfate exerts no central anticonvulsant action[1]

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ABSTRACT It was said that parenteral magnesium (MS) had a central anticonvulsant action responsible for controlling seizures in eclampsia of pregnancy. The present study was carried out to examine this statement. In conscious rabbits, MS 214 mg · kg^{-1} iv quickly relieved them from convulsion induced by sc pentylenetetrazol, yet spikes of high frequency in electrocorticogram burst unceasingly. Judging from electrocorticogram changes, MS 220 mg · kg^{-1} iv did not raise the electroshock seizure threshold. In mice, MS 430 mg · kg^{-1} did not significantly increase the LD_{50} of ip pentylenetetrazol. However, in anesthetized rats, MS 250 mg · kg^{-1} ip lowered the hypertensive response to angiotensin amide and norepinephrine. These results indicated that parenterally administered MS exerted no demonstrable central anticonvulsant action, and its benefits gained in the treatment of eclampsia of pregnancy might derive from its peripheral action, such as reduction of vascular response to pressor substances.

KEY WORDS magnesium sulfate; pentylenetetrazol; angiotensin amide; norepinephrine; anticonvulsants; electroencephalography

提要 给戊四唑诱发惊厥兔 iv 硫酸镁(MS), 只能制止抽搐, 不能制止皮层癫痫样放电. 兔 iv MS 不能提高电击致惊阈. 小鼠 sc MS 不能提高戊四唑的 LD_{50}. MS 实无中枢性抗惊厥作用. 大鼠 ip MS 可降低血管紧张素酰胺与去甲肾上腺素的升压效应. 结合文献, 提出了 MS 可能通过外周作用而发挥防治子痫效果的观点.

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关键词 硫酸镁; 戊四唑; 血管紧张素酰胺; 去甲肾上腺素; 抗惊厥药; 脑电描记术

用注射硫酸镁(MS)的方法以控制子痫及其他类型惊厥, 已历多年. 过去许多著作[1-3]认为 MS 通过其中枢抑制作用而抗惊厥. 此种观点实肇始于早年之表面观察而乏有力证据[4]. MS 中枢作用中之麻醉作用和呼吸抑制作用现已否定[5,6]. 中枢性抗惊作用也已有人怀疑[7]. 我们在兔与小鼠进行了注射 MS 中枢性及外周性抗惊作用的再评价, 并在大鼠试验了该药对血管收缩物质升压作用的影响.

MATERIALS AND METHODS

日本大耳兔 20 只, 2.47 ± SD 0.21 kg, ♀♂兼用. Wistar 种大鼠 12 只, 0.22 ± 0.04 kg, ♀♂兼用. NIH 种小鼠 150 只, 20.2 ± 1.5 g, ♀♂各半. 上述动物由我校动物科饲养、供应.

MS(上海试剂四厂, AR). 戊四唑注射液(pentylenetetrazol, 上海新亚药厂). 血管紧张素酰胺(angiotensin amide, AA, 瑞士 Ciba 药厂). 去甲肾上腺素注射液(norepinephrine, NE, 西安制药厂).

皮层脑电图(electrocorticogram)观察 切开兔头顶部皮肤, 暴露颅骨. 在双额与双顶部各置不锈钢皮层电极 1 对, 联接多道生理记录仪(SJ-41 型, 上海医用电子仪器厂), 进行皮层脑电图的观察与记录.

电击致惊阈(electroshock seizure threshold, EST)测试 在兔的两耳根各刺入针形电极 1 枚, 联接电惊厥仪(本校仪器厂), 采用 50 Hz 交流电进行电击, 每次通电 1 s. 电流强度逐次递增, 直至兔发生惊厥、皮层脑电图上爆发高频

高幅棘波(兔因给药而发生骨骼肌麻痹后，只观察皮层脑电图变化)．此时的电流强度(mA)即为 EST 之值．

血压的记录　大鼠 ip 戊巴比妥钠 45 mg · kg^{-1} 麻醉，颈动脉插管，经压力传感器，用台式平衡记录仪(上海大华仪表厂)记录血压变化．

LD_{50}　用加权概率单位分析法计算．用 t 检验法检测 LD_{50} 差别的显著性[8]．

RESULTS

MS 的抗惊厥作用

1　戊四唑诱发惊厥试验　A 组 4 只兔，sc 戊四唑 100 mg · kg^{-1} 后 7–10 min，出现阵发性惊厥．发作时骨骼肌不停抽搐，最后发展为角弓反张，皮层脑电图上显示高频高幅棘波，然后逐渐缓解．如此发作两次后，缓慢 iv MS 214 mg · kg^{-1}．兔全身肌肉松弛，抽搐停止，呼吸微弱(间或需辅以人工呼吸)，然而皮层脑电图上仍不时爆发高频高幅的癫痫波如故(Fig 1)．

B 组 4 只兔，同上以戊四唑诱发惊厥后，iv 戊巴比妥钠 25 mg · kg^{-1}．兔即停止抽搐，呈浅麻醉状态．皮层脑电图上的高频高幅棘波同时消失(Fig 1)．

2　电击诱发惊厥试验　A 组 6 只兔，给药前的 EST 为 19.5± 1.4 mA．iv MS 220 mg · kg^{-1} 后，兔呈轻瘫痪状．再测试 EST，为 19.8± 1.6 mA，与给 MS 前比较，相差不显著($P>0.05$)．

B 组 5 只兔，给药前的 EST 为 20.2± 1.8 mA．iv 苯巴比妥钠 70 mg · kg^{-1} 后 25 min，兔进入镇静状态．此时测得 EST 为 28± 3 mA，相差非常显著($P<0.01$)．

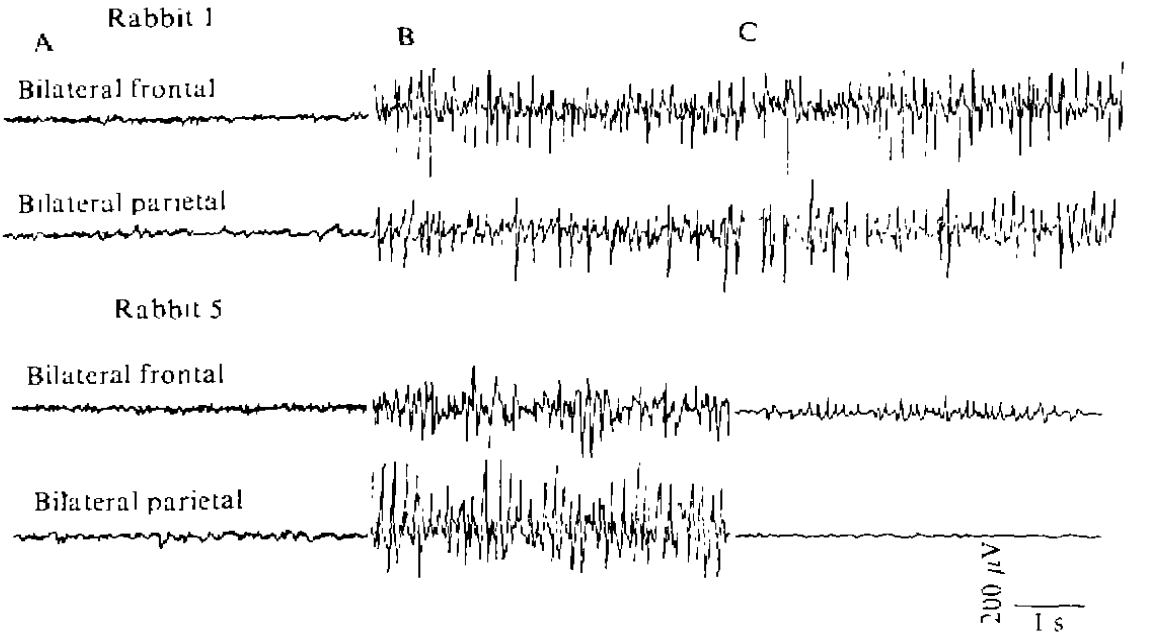

Fig 1.　Influence of magnesium sulfate (MS) administration on electrocorticogram changes induced by pentylenetetrazol in rabbit in comparison with that of pentobarbital sodium administration.　Rabbit ＃1:　A) Control;　B) after sc pentylenetetrazol 100 mg · kg^{-1}, during convulsion;　C) after iv MS 214 mg · kg^{-1} in slow bolus, convulsion stopped, yet epileptic discharges in electrocorticogram burst out repeatedly.　Rabbit ＃5:　A) Control;　B) after sc pentylenetetrazol 100 mg · kg^{-1}, during convulsion;　C) after iv pentobarbital sodium 25 mg · kg^{-1}, clonic convulsion and epileptic discharges subsided simultaneously.

注射 MS 对戊四唑 LD_{50} 的影响 小鼠 150 只，按性别、体重，随机均匀分为 3 组，按不同安排(Tab 1)给药后观察各组小鼠的反应. 48 h 后清点各组死亡鼠数并计算 LD_{50} 值. 对照组与预给 MS 组小鼠的死亡都发生在给戊四唑后最初的 45 min 内. 预给戊巴比妥钠组小鼠的死亡则有明显延迟，发生在给戊四唑 1 h 之后. 预给 MS 组的戊四唑 LD_{50} 值虽较对照组稍大，但差别不显著；而预给戊巴比妥钠组的戊四唑 LD_{50} 值则有成倍增长(Tab 1). 据此不能认为注射 MS 能对戊四唑所致死亡发挥明显保护作用.

Tab 1. Influence of pretreatment with $MgSO_4$ or pentobarbital sodium on LD_{50} of pentylenetetrazol (PT) in mice. $^{*}P>0.05$, $^{***}P<0.01$ *vs* control.

Pretreatment	Dose of PT ($mg \cdot kg^{-1}$, ip)	Mortality	LD_{50} (95% fiducial limits)
Control	140	10 / 10	97 (89–105)
	120	8 / 10	
	102	6 / 10	
	87	3 / 10	
	74	1 / 10	
$MgSO_4$ 430 $mg \cdot kg^{-1}$ + sc, 10 min before	140	9 / 10	107* (99–116)
	120	8 / 10	
	102	3 / 10	
	87	2 / 10	
	74	0 / 10	
Pentobarbital sodium 41 $mg \cdot kg^{-1}$ sc, 10 min before	300	10 / 10	194*** (171–218)
	240	7 / 10	
	192	4 / 10	
	154	2 / 10	
	123	1 / 10	

+Dose enough to make most mice unable to right up.

注射 MS 对两种缩血管物质升压作用的影响

1 *MS 对 AA 升压作用的影响* 戊巴比妥钠 45 $mg \cdot kg^{-1}$ ip 麻醉大鼠 6 只，iv AA 4 与 8 $\mu g \cdot kg^{-1}$ 引起的血压升高%分别为 37±8%与 52± 12%. ip MS 250 $mg \cdot kg^{-1}$ 30 min 后，iv 相同剂量 AA 引起的血压升高%分别为 24±4%与 29±5%，相差显著(Tab 2)，提示注射 MS 能降低血管平滑肌对血管紧张素类物质的反应性.

Tab 2. Modification of hypertensive effect of iv angiotensin amide (AA) or norepinepharine (NE) by ip $MgSO_4$ (MS) 250 $mg \cdot kg^{-1}$ in pentobarbital anesthetized rats. $n=6$, $\bar{x} \pm SD$. $^{**}P<0.05$, $^{***}P<0.01$ *vs* "Before MS"

Drug ($\mu g \cdot kg^{-1}$)		Basal BP (kPa) Before MS	Basal BP (kPa) After MS	% of BP elevation Before MS	% of BP elevation After MS
AA	4	14.6±1.9	13.9±0.9	37±8	24±4**
	8	14.3±1.6	13.7±1.0	52±12	29±5**
NE	8	15.4±1.5	14.3±1.1	24±6	17±4**
	16	15.2±1.2	14.2±1.3	37±8	23±3***

2 *MS 对 NE 升压作用的影响* 同上麻醉大鼠 6 只，iv NE 8 与 16 $\mu g \cdot kg^{-1}$ 引起的血压升高%分别为 24±6%与 37±8%. ip MS 250 $mg \cdot kg^{-1}$ 30 min 后，iv 相同剂量 NE 引起的血压升高%分别为 17±4%与 23±3%，相差显著(Tab 2)，提示注射 MS 能降低血管平滑肌对 NE 的反应性.

DISCUSSION

本文结果表明，无论对于化学物质或电流刺激所诱发的惊厥，注射 MS 都只能依赖其神经肌接头阻滞作用[4,6]，消除惊厥的外观表现，不能阻止中枢神经系统的强烈兴奋及其严重后果. 这样看来，传统上所谓镁盐具有中枢性抗惊厥作用，将它当作为一种抗惊厥药[2,3]，实属误解.

应加说明的是我们对于 MS 中枢性抗惊厥作用的否定并不同时意味着对它在防治子痫方面卓越功效[9]的否定. 我们推想该药对子痫的疗效或许另有其作用依据. 目前普遍认为在子痫发作之前，先有肾上腺-胎盘-肾脏间稳态机制失控，其中肾素与血管紧张素产生增加

与心血管系统对 NE 与血管紧张素反应性的增高在子痫的发病机制中有重要意义[10,11]. 过去已经有人证明在离体条件下提高营养液中 Mg^{2+}的浓度可以降低血管平滑肌对 NE 与血管紧张素的反应性[12], 现在我们又在整体动物实验中予以进一步证实. 故此我们认为镁盐治疗子痫的主要作用部位不在中枢而在外周, 而其降低血管平滑肌对缩血管物质反应性的作用可能占有重要地位.

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中国药理学报 *Acta Pharmacologica Sinica* 1991 Mar; 12 (2): 155–159

4–氨基吡啶诱发小鼠的激怒反应[1]

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4–Aminopyridine induced rage reaction in mice[1]

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ABSTRACT Rage reaction was induced in mice by sc 4–aminopyridine (4–AP) 6 mg · kg^{-1}. Mice appeared hyperreactive after 8–12 min and then squeaked and fought each other. These manifestations were most distinct in 10–30 min and subsided after 40–60 min. The occurrence of rage reaction on this dose level was around 90%. At higher doses 4–AP caused convulsions and death after evocation of rage reaction. The ED_{50} of 4–AP for eliciting rage reaction was 4.7 ± 0.7 mg · kg^{-1} sc. No significant difference in induction of rage reaction was seen