Effects of Intracerebroventricular Administration of Magnesium Sulphate on Blood Pressure and Heart Rate in Anesthetized Normotensive and Hypertensive Rats

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Abstract—Intracerebroventricular (i.c.v.) injection of magnesium sulphate (MgSO₄: 2.5, 5 and 10 μmol in 5 μl) decreased blood pressure and heart rate in both anesthetized normotensive (WKY) and hypertensive rats (SHR). The effects were greater in WKY than in SHR. Moreover, a pretreatment with hexamethonium (2 mg/kg, i.v.) significantly blunted the hypotensive and bradycardic effects induced by i.c.v. injection of 10 μmol of MgSO₄ in both WKY and SHR. Our data suggest that MgSO₄ produces hypotensive and bradycardic effects when injected i.c.v. in both WKY and SHR.

It has been demonstrated that intravenous injection of magnesium salts lowers blood pressure and heart rate in both laboratory animals and human beings (1, 2). Moreover, magnesium has been used in the management of vasospastic angina (3) and to aid the control of catecholamine-induced cardiovascular disturbances of tetanus (4) and pheochromocytoma (5). Despite this wide usage, the mechanism of action of magnesium is still far from being completely understood. Magnesium has well-established vasodilator effects in vitro and in vivo (6), but the hypotensive effect seems to be transitory, and myocardial depression may be required for the maintenance of magnesium-induced hypotension. In light of these observations, we investigated whether an i.c.v. injection of magnesium sulphate lowers blood pressure and heart rate in anesthetized normotensive and hypertensive rats. This experiment may provide indirect evidence for a central nervous system (CNS) involvement in the cardiovascular effects induced by intravenous administration of magnesium salts.

Male spontaneously hypertensive rats (SHR) and male normotensive rats derived from the WKY strain weighing 225–250 g and aged 12 weeks were used in this experiment. Rats were anesthetized with urethane (1.3 g, i.p.) and placed in a stereotaxic instrument. A burr hole was drilled in the skull 1.5 mm lateral to the bregma; and a cannula consisting of two concentric stainless steel tubes, a 1.6-cm long, 23 gauge outer tube (guide cannulae) and an inner tube (o.d., 0.2 mm), used for infusion, was inserted through the hole to a depth of 35 mm below the cortex. To directly record blood pressure and to facilitate intravenous injection, catheters (PE 50) were implanted into the left common carotid artery and into the right jugular vein as described elsewhere (7). The arterial catheter was connected to a pressure transducer, the pressure pulse triggered a cardio-tachometer, and both blood pressure and heart rate (HR) were displayed on a polygraph. Mean arterial blood pressure (MAP) and HR were recorded in mmHg and beats/min, respectively. At the completion of the experiment, dye was injected in each animal through the cerebral ventricle to confirm the injection site.

Magnesium sulphate, magnesium chloride, hexamethonium chloride and sodium nitroprusside were obtained from Sigma. All
Table 1. Effects of intracerebroventricular (i.c.v.) injection of magnesium sulphate on mean arterial blood pressure (MAP) and heart rate (HR) in normotensive (WKY) and hypertensive (SHR) rats

| Treatment          | MAP (mmHg) | HR (beats/min) |
|--------------------|------------|----------------|
|                    | WKY before | WKY after      | SHR before | SHR after      |
| Saline, 6 µl, i.c.v. | 86±3.9    | 88±4.1         | 133±3.7    | 130±2.9        | 319±3.9    | 321±2.8        | 393±4.6    | 392±3.8        |
| MgSO₄, 2.5 µmol, i.c.v. | 88±2.1   | 77±2.6*        | 130±2.9    | 118±2.1*       | 322±4.2    | 300±3.2*       | 390±2.7    | 365±4.5*       |
| MgSO₄, 5.0 µmol, i.c.v. | 87±4.1   | 66±2.9**       | 132±2.5    | 109±3.3*       | 319±2.5    | 266±3.2**      | 380±4.7    | 336±3.9*       |
| MgSO₄, 10 µmol, i.c.v. | 89±3.2   | 60±2.2†        | 131±4.4    | 100±2.6**      | 326±3.2    | 245±2.3†       | 385±5.6    | 315±4.2**      |
| Hexam, 2 mg/kg, i.v. | 88±4.1   | 82±3.9         | 128±4.2    | 122±3.2        | 315±4.1    | 310±3.1        | 378±4.2    | 368±4.2        |
| Hexam, 2 mg/kg, i.v. | 82±3.3   | 79±3.2*        | 121±3.3    | 117±2.8*       | 328±3.1    | 315±4.7*       | 376±5.1    | 365±4.4*       |
| +MgSO₄, 10 µmol, i.c.v. |           |                |            |                |            |                |            |                |

Each point represents the mean±S.E.M. of six experiments. The volume injected i.c.v. was always 5 µl. The volume injected i.v. was 0.1 ml/100 g body weight. Hexam.=Hexamethonium. Hexamethonium was injected i.v. 5 min prior MgSO₄. *P<0.05 vs. the value before i.c.v. injection; **P<0.01 vs. the value before i.c.v. injection; †P<0.005 vs. the value before i.c.v. injection; ‡P<0.001 vs. corresponding MgSO₄, 10 µmol.
the drugs were dissolved in 0.9% NaCl solution (saline). Each animal received only one dose of the drug. The data are expressed as the mean±S.E.M. Results were subjected to multigroup analysis of variance (ANOVA) to determine if the data were significantly different (P<0.05).

I.c.v. injection of magnesium sulphate (2.5, 5 and 10 μmol in 5 μl) significantly decreased mean arterial blood pressure and heart rate in both WKY and SHR (Table 1 and Fig. 1). The hypotensive and bradycardic effect started immediately after i.c.v. injection of MgSO₄ and lasted for 25 min (Fig. 1). Similar results were obtained when we i.c.v. injected 2.5, 5 and 10 μmol of magnesium chloride (results not shown). The highest dose of magnesium sulphate (10 μmol), injected intravenously, did not modify MAP and HR in both WKY and SHR. In WKY, basal MAP and HR were, respectively, 88±3.6 mmHg and 320±5.4 beats/min before i.v. injection of magnesium and 90±4.6 mmHg and 325±4.4 beats/min after i.v. administration of magnesium. In SHR, basal MAP and HR averaged, respectively, 131±3.9 mmHg and 388±3.5 beats/min before i.v. magnesium and 128±4.1 mmHg and 390 beats/min after i.v. injection of magnesium. Furthermore, the hypotensive and bradycardic effects induced by central administration of magnesium sulphate were greater in WKY than in SHR (Table 1 and Fig. 1). As a matter of fact, 5 μmol of magnesium sulphate decreased MAP by 24% in WKY and by 17% in SHR, respectively (Fig. 1). Magnesium induced hypotensive and bradycardic effects were also abated by a pretreatment with hexamethonium (2 mg/kg), injected i.v. 5 min prior magnesium sulphate (Table 1). Moreover, hexamethonium pretreatment, by itself, slightly but not significantly decreased basal MAP and HR in both WKY and SHR.

Our data indicate that central administration of magnesium sulphate lowers blood pressure and heart rate in both normotensive and hypertensive rats. Therefore, it could be speculated that the depressor and bradycardic effects induced by i.v. magnesium salts infusion are, at least in part, due to changes in the function of the autonomic nervous system. The cardiovascular responses following i.c.v. injection of magnesium sulphate were greater in WKY than in SHR, thus suggesting that magnesium in the CNS might be involved in the control of experimental hypertension.

In our experiment, injection of both magnesium sulphate and magnesium chloride produced similar cardiovascular effects: this clearly indicates that the cardiovascular effects observed after i.c.v. injection of
magnesium sulphate are not due to the sulphate. Moreover, since the highest dose of magnesium sulphate, injected i.v., did not modify MAP and HR, a magnesium peripheral effect, due to its leakage into the peripheral circulation, can be ruled out. It has been demonstrated that i.c.v. injection of L-glutamate, a brain excitatory aminoacid which acts on NMDA receptors (8), increases blood pressure and heart rate in the rat by enhancing sympathetic outflow (9). Magnesium has also been shown to block, in a voltage dependent way, the NMDA receptors (10). In light of these findings, it could be argued that in our experiment, magnesium sulphate inhibits NMDA receptors in turn decreasing sympathetic outflow and blood pressure.

In conclusion, whatever the mechanism, as far as we know, this is the first report indicating that magnesium elicits hypotensive and bradycardic effects when injected i.c.v. in normotensive and hypertensive rats.

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