# Site of Action of Magnesium in Treatment of Some Toxic Effects Produced by TEPP.* (22079)

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Major pharmacological actions of magnesium have been discussed in recent reviews, Engbaek(1); Smith, Winkler and Hoff(2). Various peripheral and central effects of the ion have been described, but, as noted by Engbaek(1), the question of relative sensitivities of central and peripheral structures to magnesium has not been settled.

It has been reported, McNamara, Koelle and Gilman(3), that magnesium sulfate, when used adjunctively with pentobarbital and atropine, is of value in treating poisoning produced by diisopropylfluorophosphate (DFP). The current investigation is an attempt to elucidate the site of action of magnesium in the treatment of certain effects produced by tetraethylpyrophosphate (TEPP).

*Methods.* Three types of experiments were performed. 1) Cats were anesthetized with sodium pentobarbital (30 mg/kg, i.p.), atropinized (1 mg/kg, i.m.) and respired artificially. Sciatic and femoral nerves of one leg were sectioned, and identical bi-polar platinum electrodes were inserted into the gastrocnemius muscles of this leg and of the opposite intact leg. Electrical activity of these muscles was recorded with a Grass electroencephalograph. In some of these experiments, electroencephalograms were recorded from screw electrodes placed in the skull. Recordings were made immediately prior to, and periodically after, poisoning with tetraethylpyrophosphate (TEPP) by injection of 0.3 to 2.0 mg/kg into the antibrachial vein. When skeletal muscle fasciculations had been produced by TEPP, magnesium sulfate or magnesium chloride (30-100 mg/kg in 5% solution) was injected intravenously. In a few experiments, after fasciculation had been abolished by the magnesium salt, the threshold for indirect stimulation of the gastrocnemius muscle of the intact leg was compared with that at the beginning of the experiments. 2. The sciatic nerve-gastrocnemius muscle technic of Wolff and Cattell (4) was used to study the response of muscle to supramaximal excitation of its motor nerve following intravenous doses of 30-130 mg/kg of magnesium sulfate in cats. 3) Rabbits were paralyzed by Intocostrin (1-2 units/kg i.v.) and were respired artificially. Dibutoline (0.5 mg/kg, i.m.) was administered because it is the authors' experience that this drug minimizes bronchial and cardiovascular effects of TEPP without preventing appearance of the "grand mal" type of electroencephalogram produced by the latter com-

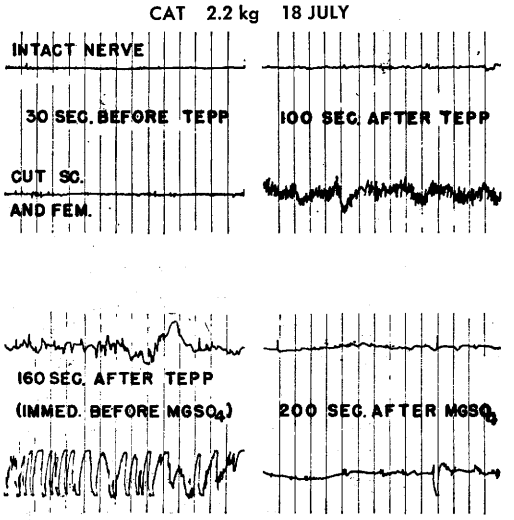


FIG. 1. Effect of magnesium sulfate (30 mg/kg i.v.) on fasciculation induced by TEPP (1 mg/kg i.v.) in cat gastrocnemius with intact innervation (upper traces) and with denervation approximately 2 hr before experiment (lower traces). Cat received atropine (1 mg/kg i.v.) about 2 hr before experiment, and given artificial respiration as necessary after poisoning. Tracings shown are similar to those obtained from 9 other cats treated similarly.

* Abstract of this work appears in *Fed. Proc.*, 1955, v14, 373.

TABLE I. Effect of Magnesium on Response of Gastrocnemius Muscle to Supramaximal Electrical Stimulation of Its Motor Nerve.

| Cat No. | Dose $MgSO_4$ (mg/kg, i.v.) | Effect on contraction height |
|---|---|---|
| 1 | 30 | No significant effect |
| | 100 (Immed.)* | About 70% reduction |
| 2 | 30 | No significant effect |
| | 100 (immed.) | Complete block |
| 3 | 50 | No significant effect |
| | 50 (Immed.) | About 85% reduction |
| 4 | 50 | No significant effect |
| | 50 (Immed.) | About 50% reduction |
| 5 | 50 | No significant effect |
| | 50 (Immed.) | Complete block |
| 6 | 60 | No significant effect |
| 7 | 60 | About 30% reduction |
| 8 | 120 | " 85% " |

* Immed. = Immediately after 1st dose.

pound. A screw electrode was placed in the right frontal area of the skull, potential differences between this point and an indifferent skin area being recorded. TEPP was then administered. When increased electrical activity of the brain resulted, magnesium sulfate (30-150 mg/kg, i.v.) was administered in an effort to counteract the central effects of TEPP. Atropine (1-3 mg/kg, i.v.) was injected thereafter.

*Results.* Group I. Fig. 1 shows clearly that the site of action of magnesium in counteracting these fasciculations is peripheral because magnesium sulfate, in a dose of 30 mg/kg i.v., quickly abolished the fasciculatory response in both the decentralized leg and the leg with intact nerves. In other experiments, doses of up to 100 mg/kg of magnesium salt were needed to abolish fasciculation. In 4 of 5 experiments, it was noted that the threshold for indirect stimulation of the muscle following abolition of fasciculation by low doses of magnesium was similar to that of the prepoisoning control.

Group II. Table I illustrates the effect of magnesium sulfate on the response of the gastrocnemius muscle to supramaximal electrical stimulation of the sciatic nerve. Doses of magnesium (30 mg/kg, i.v.) which frequently abolished fasciculations in other experiments did not alter significantly the response of the muscle to motor nerve excitation. Large doses of the magnesium ion, however, reduced the muscles' contraction height.

Group III. Magnesium sulfate in doses as high as 150 mg/kg, i.v., did not abolish the abnormal brain activity in any of 6 rabbits. When atropine sulfate was then given (1-3 mg/kg, i.v.), the "grand mal" pattern was quickly abolished. Fig. 2 illustrates these results.

*Discussion.* The results of this investigation show that the site of action of magnesium sulfate in the treatment of some effects of TEPP intoxication is primarily peripheral. The magnesium salt was effective in abolishing fasciculations in both the leg with sectioned nerves and in that with intact innervation. The exact mechanism of this action has not been elucidated by the current experiments, but evidence has been obtained that the magnesium effect does not involve necessarily depression of neuromuscular transmission or of repetitive cerebral or spinal cord activity. The action probably is localised, therefore, to the skeletal muscle fiber.

It has been reported that magnesium reduces the output of acetylcholine from cholinergic nerve endings, Hutter and Kostial(5). Others, Del Castillo and Engbaek(6), have demonstrated that, although the main effect of magnesium on neuromuscular function is a diminution of the amount of acetylcholine released by the motor nerve endings, the magnesium ion raises the electrical threshold of the muscle membrane and also has a small depressant effect on the acetylcholine sensitivity of the end-plates. Both of these mechanisms may well play a part in the effect on the muscle fiber made to fasciculate by TEPP.

*Summary.* 1. The primary site of action of magnesium in the treatment of skeletal muscle fasciculations produced during TEPP intoxication is peripheral. 2. Magnesuim apparently has little, if any, value in the treatment of the central effects produced by this poison.

1. Engbaek, L., *Pharmacol. Rev.*, 1952, v4, 396.

2. Smith, P. K., Winkler, A. W., and Hoff, H. E., *Anesthesiology*, 1942, v3, 323.

3. McNamara, B. P., Koelle, G. B., and Gilman,

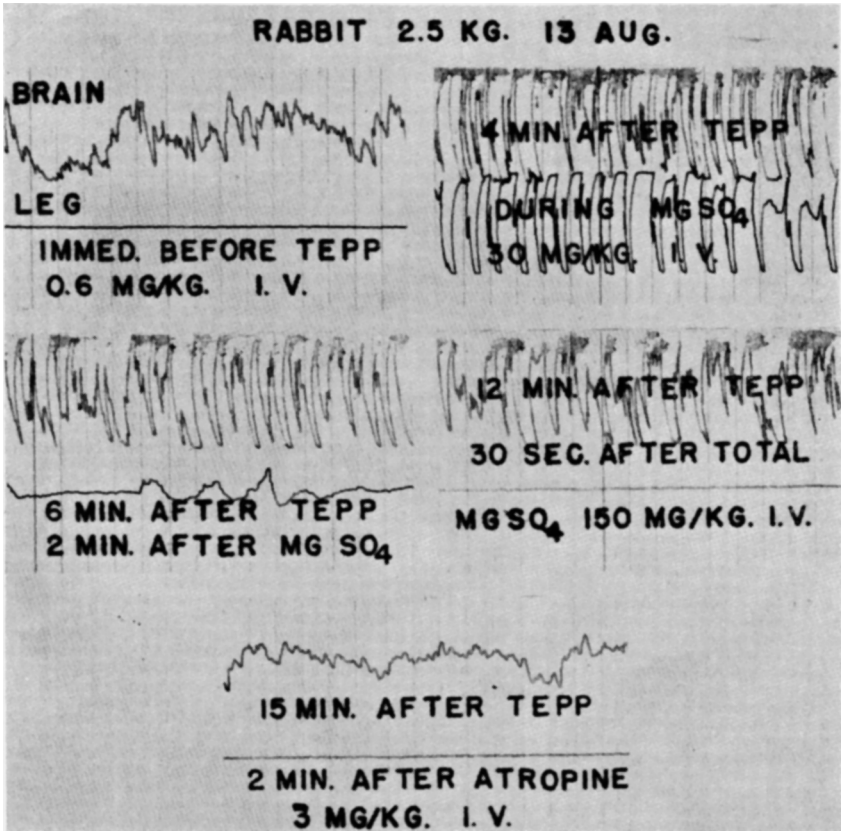


FIG. 2. Comparative effectiveness of magnesium sulfate (30 mg/kg i.v. and 7.5 min. later 120 mg/kg i.v.) on EEG hyperactivity (upper traces) and on fasciculation of gastrocnemius (lower traces) induced by TEPP (0.6 mg/kg i.v.) and comparative effectiveness of magnesium sulfate and of atropine sulfate (3 mg/kg) on EEG hyperactivity (last two panels). Rabbit received Dibutoline (0.5 mg/kg i.m.) and Intocostrin (2 units/kg i.v.) before start of experiment, and respired artificially throughout experiment.

A., *J. Pharmacol. Exp. Therap.*, 1946, v88, 27.

4. Wolff, H. G., and Cattell, McK., *Arch. Neurol. Psychiat.*, 1934, v32, 81.

5. Hutter, O. F., and Kostial, K., *J. Physiol.*, 1953, v120, 53.

6. Del Castillo, J., and Engbaek, L., *J. Physiol.*, 1953, v120, 54.

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