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Enhancement of Apomorphine and *l*-Amphetamine-Induced Behaviors by Magnesium[1]

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KANTAK, K. M. AND L. K. ADLERSTEIN. *Enhancement of apomorphine and l-amphetamine-induced behaviors by magnesium.* PHARMACOL BIOCHEM BEHAV **36**(1) 29–33, 1990.—The behavioral effects of magnesium suggest that this divalent cation has psychomotor stimulant-like properties. Because deficiencies of this cation lead to reductions in drug-induced behaviors dependent on the levels of norepinephrine and dopamine, and numerous in vitro studies have demonstrated a relationship between magnesium and catecholamine activity, the present experiments investigate whether administration of magnesium will lead to increases in stereotyped and locomotor behaviors induced by apomorphine and *l*-amphetamine. Such changes would suggest that magnesium is increasing the activity of catecholamines in vivo. The results demonstrate that magnesium dose dependently increases the potency of these drugs by producing greater behavioral effects at certain drug doses, by producing shifts to the left in dose-response functions, and by producing decreases in the ED_{50} as dose of magnesium increases.

Apomorphine *l*-Amphetamine Magnesium Motor activity Stereotypy Norepinephrine Dopamine

MAGNESIUM (Mg^{2+}) alterations have been shown to exert various effects on aggressive behavior. Restriction of dietary Mg^{2+} to 15% or 25% of the daily requirement led to reductions in offensive aggression in male mice (13). Male mice receiving acute injections of 15, 30, 60 or 125 mg/kg magnesium chloride ($MgCl_2$) showed dose-dependent changes in offensive threat and attack: lower doses produced increases in behavior and higher doses produced decreases (12). Further studies on mouse aggression demonstrated that $MgCl_2$ dose dependently potentiated the dose-dependent effects of cocaine and attenuated the dose-dependent effects of haloperidol (14). Opposite results were obtained with a 15% required-Mg^{2+}-deficient diet. Tolerance did develop to the chronic administration of $MgCl_2$ in that the enhancement in aggression was no longer present after 4 days of injections with 30 mg/kg and after 15 days of injections with 15 mg/kg (12). Taken together, these data suggest a possible stimulant-like action to $MgCl_2$ because of the similarities in the behavioral effects on aggression and shape of the dose-response functions (8, 15, 21–23, 28).

Apomorphine, a DA agonist, produces stereotyped behavior that is DA-mediated and includes repetitive sniffing, licking, and gnawing (5). *l*-Amphetamine enhances NE activity in low doses and DA activity in high doses (3, 11, 24). It can produce a stimulation in locomotor activity, which includes rearing and forward locomotion, with doses that enhance NE activity or with doses that enhance DA activity (20,27). If an animal has altered DA or NE activity, then the intensity of these behavioral responses upon drug administration is changed. In mice exposed to various Mg^{2+}-deficient diets, such functional changes have been assessed using apomorphine-induced stereotyped behavior as an index of DA activity and low dose *l*-amphetamine-induced motor behavior as an index of NE activity (13). The diets produced concentration-dependent and time-dependent reductions in apomorphine-induced sniffing with an associated increase in the number of bouts of sniffing, and reductions in *l*-amphetamine-induced locomotion and rearing. Similar methods have been successfully applied with other nutritional variables (1,18).

The purpose of the present study was to determine whether there was a functional change in dopamine (DA) and norepinephrine (NE) activity with aggression-altering doses of $MgCl_2$ because there are 1) relationships between brain catecholamines and aggression (17); 2) relationships between Mg^{2+} and catecholamine activity (10, 19, 25, 26, 30, 32); and 3) relationships between stimulant actions of drugs and brain catecholamines (4).

METHOD

Experiment 1. $MgCl_2$ Treatments and Apomorphine Stereotypy

Animals. Seventy-five naive CFW male mice (Charles River, Portage, MI), 42 days old, were housed 5 per polycarbonate cage

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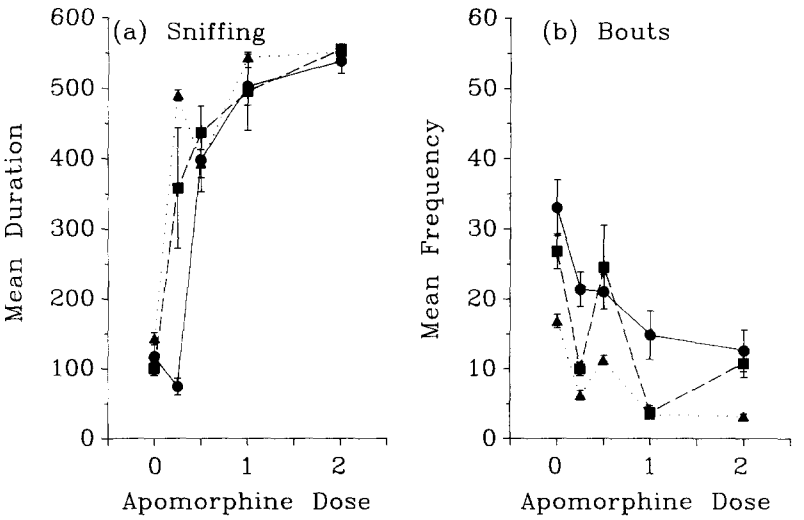

FIG. 1. Mean ± S.E.M. duration of sniffing in sec (a) and the number of bouts of sniffing (b) immediately following 0, 0.25, 0.5, 1.0 and 2.0 mg/kg apomorphine in mice pretreated 5 min before 10 min of testing with either 0 (circles), 30 (squares) or 125 (triangles) mg/kg $MgCl_2$.

measuring 6.5 × 5.25 × 11 in. Wood shavings covered the floor of the cage and the cage top was covered with a stainless steel lid. Room temperature was maintained at 27°C with lights on from 8:00 a.m. to 8:00 p.m. daily. The mice were given free access to Rat/Mouse Purina Chow and water.

Drugs. Apomorphine hydrochloride (APO; Sigma, St. Louis, MO) was used to stimulate DA activity. Five doses of APO were used: 0 (distilled water), 0.25, 0.5, 1.0 or 2.0 mg/kg. APO was dissolved in 10 ml of distilled water and injected intraperitoneally just prior to testing. Magnesium chloride ($MgCl_2 \cdot 6H_2O$; Fisher Scientific, Medford, MA) was given in 3 anhydrous doses: 0 (0.9% NaCl), 30, or 125 mg/kg. $MgCl_2$ was dissolved in 10 ml distilled water and injected subcutaneously 5 min before testing. All injection volumes were 1 ml/100 g body weight.

Procedure. The 75 mice were divided into 3 groups of 25 animals. Each group of 25 was assigned to a pretreatment dose of $MgCl_2$: 0, 30 or 125 mg/kg. Each of the pretreatment groups was further divided into 5 subgroups of 5 mice each. Each subgroup was administered a different dose of APO: 0, 0.25, 0.5, 1.0 or 2.0 mg/kg. Thus, there were 5 mice per drug and dose combination and each mouse was used only once in testing.

Following the $MgCl_2$ injection, mice were placed back into the home cage for 5 min. Immediately following the APO injection, mice were placed into a test cage similar in construction and dimensions to the home cage. The top of the cage was covered with a flat Plexiglas lid with several airholes. Over the next 10 min the duration of sniffing and frequency of bouts of sniffing were recorded by timers and counters mounted on a lap board. Sniffing was defined as horizontally directed movements associated with head bobbing which was directed at the floor of the cage. When head bobbing was absent, or when movements were not horizontal and directed at the floor of the cage, these were considered breaks in stereotypy and also defined the end of a bout of sniffing.

Experiment 2. $MgCl_2$ Treatments and l-Amphetamine Motor Activity

Animals. One hundred and thirty-five mice, maintained in a manner similar to those in Experiment 1, were used in this experiment.

Drugs. The same $MgCl_2$ doses were used in this experiment: 0, 30 or 125 mg/kg and were injected 5 min before testing. Nine doses of *l*-amphetamine sulfate (*l*-AMPH; Smith, Kline and French, Philadelphia, PA) were used: 0 (0.9% NaCl), 0.25, 0.5, 1.0, 1.5, 6.0, 12.0, 20.0 or 40.0 mg/kg. *l*-AMPH was dissolved in 10 ml of 0.9% NaCl and injected intraperitoneally 40 min prior to testing. All injection volumes were 1 ml/100 g body weight.

Procedure. The 135 mice were divided into 3 groups of 45 animals. Each group of 45 was assigned to a pretreatment dose of $MgCl_2$: 0, 30 or 125 mg/kg. Each of the pretreatment groups was further divided into 9 subgroups of 5 mice each. Each subgroup was administered a different dose of *l*-AMPH: 0, 0.25, 0.5, 1.0, 1.5, 6.0, 12.0, 20.0 or 40.0 mg/kg. Thus, there were 5 mice per drug and dose combination and each mouse was used only once in testing.

Following the *l*-AMPH injection, mice were placed into the test cage for 40 min prior to the start of testing in order to observe peak effects of *l*-AMPH on locomotion. The test cage was identical to that used in Experiment 1. Five min before the end of this 40-min period, mice were injected with $MgCl_2$. Mice were placed directly into the test cage after *l*-AMPH administration to allow habituation to the new environment so that drug effects on locomotion could be separated from the effects of a novel environment on locomotion. During the 10-min test session, the duration of locomotion and frequency of rears were recorded by timers and counters mounted on a lap board. Locomotion was defined as forward horizontal movements which resulted in displacement of the body. A rear was defined as a full upright extension of the body, either along the wall of the cage or in the middle of the cage.

RESULTS

Experiment 1. Mg^{2+} Treatments and Apomorphine Stereotypy

Analysis of the sniffing duration data revealed significant effects due to dose of APO, $F(4,60) = 104$, $p<0.001$. In general, the dose-response function for APO was sigmoidal, with high doses being more effective and lower doses being less effective (Fig. 1a). Besides sniffing duration differing as a function of APO dose, it differed overall as a function of $MgCl_2$ pretreatment dose,

TABLE 1

ED_{50} VALUES AND CORRELATION COEFFICIENTS FOR BEHAVIORS INDUCED BY APOMORPHINE AND *l*-AMPHETAMINE AND FOLLOWING DIFFERENT DOSES OF $MgCl_2$

	Apomorphine Sniffing		*l*-Amphetamine Locomotion		*l*-Amphetamine Rearing	
$MgCl_2$ Dose	ED_{50}	r	ED_{50}	r	ED_{50}	r
0	0.40	.84	8.7	.95	6.1	−.92
30	0.11	.81	4.2	.93	0.6	−.54
125	0.06	.70	6.7	.94	0.0	−.85

$F(2,60) = 14.4$, $p<0.001$. $MgCl_2$ 125 mg/kg produced the greatest average amount of sniffing with 424 sec; $MgCl_2$ 30 mg/kg produced the middle most average amount of sniffing with 389 sec; and $MgCl_2$ 0 mg/kg produced the least average amount of sniffing with 326 sec. These differences were significantly different from one another, $p<0.01$. Administration of APO and $MgCl_2$ significantly interacted to produce differences in the amount of APO-induced sniffing as a function of dose of both drugs, $F(8,60) = 10.1$, $p<0.001$. At a dose of 0.25 APO, there were significant differences in the amount of sniffing measured in the different $MgCl_2$ pretreatment groups, with 125 mg/kg producing more sniffing than 30 mg/kg which produced more sniffing than the 0 mg/kg pretreatment group, $p<0.01$. These data suggest that an increase in APO potency is produced by increasing doses of $MgCl_2$. Determination of the ED_{50} for half maximal stimulation of the control level of sniffing via linear regression analysis of each dose effect curve revealed a dose-dependent decrease in the ED_{50} as dose of $MgCl_2$ increased (Table 1). These data suggest that $MgCl_2$ shifts the dose-effect curve of APO to the left.

Analysis of the number of bouts of sniffing supports the conclusion that more APO-induced stereotypy is produced by increasing doses of $MgCl_2$. There is a significant decrease in the number of bouts of sniffing as dose of APO is increased, $F(4,60) = 29.2$, $p<0.001$, indicating that as stereotypy gets more intense, there are less bouts or interruptions in the behavior (Fig. 1b). Overall, there were significant differences in the $MgCl_2$ pretreatment groups: $MgCl_2$ 125 mg/kg produced the least average number of bouts of sniffing with 7 bouts; $MgCl_2$ 30 mg/kg produced the middle most average number of bouts of sniffing with 14 bouts; and $MgCl_2$ 0 mg/kg produced the greatest average number of bouts of sniffing with 20 bouts. These differences were significantly different from one another, $p<0.01$. There was no significant interaction because the dose effects of $MgCl_2$ did not depend upon the dose of APO being tested.

Experiment 2. Mg^{2+} Treatments and l-Amphetamine Motor Activity

Analysis of the duration of locomotion revealed significant differences due to dose of *l*-AMPH, $F(8,108) = 46$, $p<0.001$. There were biphasic dose effects of *l*-AMPH on locomotion in 0 mg/kg $MgCl_2$ control mice (Fig. 2a). There was a small, but significant peak of activity with 1.5 mg/kg, and a large significant peak of activity with 20 mg/kg, $p<0.01$ compared to the 0 mg/kg *l*-AMPH dose. Given the dose-response relation between *l*-AMPH and NE and DA release (3,11), the first smaller peak corresponds to an enhancement of NE function, and the second larger peak corresponds to an enhancement of DA function. Besides locomo-

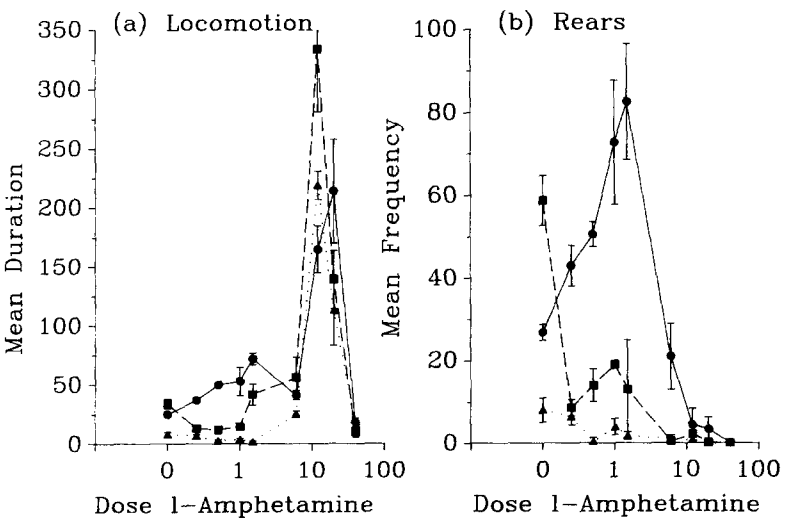

FIG. 2. Mean ± S.E.M. duration of locomotion in sec (a) and the number of rears (b) 40 min following 0, 0.25, 0.5, 1.0, 1.5, 6.0, 12.0, 20.0 and 40.0 mg/kg *l*-amphetamine (log scale) in mice pretreated 5 min before 10 min of testing with either 0 (circles), 30 (squares) or 125 (triangles) mg/kg $MgCl_2$.

tion differing as a function of dose of *l*-AMPH, it differed as a function of $MgCl_2$ pretreatment dose, $F(2,108)=6.7$, $p<0.002$. $MgCl_2$ 125 mg/kg produced overall the least average amount of locomotion with 42 sec; $MgCl_2$ 30 mg/kg produced an amount of locomotion which overall averaged 72 sec and was similar to $MgCl_2$ 0 mg/kg which produced an amount of locomotion which overall averaged 74 sec. These differences were significantly different from $MgCl_2$ 125 mg/kg, $p<0.01$. Administration of *l*-AMPH and $MgCl_2$ significantly interacted to produce difference in the amount of *l*-AMPH-induced locomotion as a function of dose of both drugs, $F(16,108)=3.5$, $p<0.001$. At a dose of 1.5 mg/kg *l*-AMPH, which produced the first significant peak in locomotion in the 0 mg/kg $MgCl_2$ pretreatment group, a sustained inhibitory effect of *l*-AMPH + 125 mg/kg $MgCl_2$ was measured, $p<0.05$. As locomotion was declining in the 0 mg/kg $MgCl_2$ group with 6 mg/kg *l*-AMPH, locomotion was beginning to increase in the 30 and 125 mg/kg $MgCl_2$ groups, such that with 12 mg/kg *l*-AMPH, there were significantly greater increases in locomotion in those groups compared to the 0 mg/kg $MgCl_2$ group, $p<0.01$ and 0.05, respectively. At a dose of 20 mg/kg *l*-AMPH, which produced the second significant peak in locomotion in the 0 mg/kg $MgCl_2$ pretreatment group, inhibitory effects of *l*-AMPH were measured in the 30 and 125 mg/kg $MgCl_2$ groups, $p<0.05$ and 0.01, respectively. This pattern of change in the dose-response functions suggests an increase in *l*-AMPH potency and leftward shift in the dose response with both doses of $MgCl_2$, particularly with doses of *l*-AMPH which influence the DA system (>6 mg/kg). Determination of the ED_{50} for half maximal stimulation of the control level of locomotion via linear regression analysis of the ascending portion of each dose effect curve revealed decreases in the ED_{50} with doses of 30 and 125 mg/kg $MgCl_2$ compared to 0 mg/kg (Table 1).

The rearing response was also affected differentially by dose of *l*-AMPH, $F(8,108)=29$, $p<0.001$, and dose of $MgCl_2$, $F(2,108)=89$, $p<0.001$. In the 0 mg/kg $MgCl_2$ control group, an inverted-U-shape response was obtained, with *l*-AMPH doses of 0.25, 0.5, 1.0, and 1.5 mg/kg producing significant increases in rearing, and doses of 12, 20 and 40 mg/kg producing significant decreases in rearing compared to the 0 mg/kg *l*-AMPH dose, $p<0.01$ (Fig. 2b). $MgCl_2$ 125 mg/kg produced overall the least average amount of rearing with 2.4 rears; $MgCl_2$ 30 mg/kg produced an intermediate amount of rearing which overall averaged 12.7 rears, and $MgCl_2$ 0 mg/kg produced the highest amount of rearing which overall averaged 33 rears. These differences for 30 and 125 mg/kg were significant compared to $MgCl_2$ 0 mg/kg, $p<0.01$. The combination of drugs significantly interacted, $F(16,108)=12.7$, $p<0.001$, to produce differences in rearing as a function of doses of both drugs. $MgCl_2$ 30 mg/kg initially increased rearing, $p<0.01$, while 125 mg/kg initially decreased rearing, $p<0.01$, compared to $MgCl_2$ 0 mg/kg. At doses of *l*-AMPH which enhanced rearing, 0.25, 0.5, 1.0 and 1.5, $MgCl_2$ 30 and 125 mg/kg significantly reduced rearing, $p<0.01$. These data suggest a leftward shift in the dose response with increasing doses of $MgCl_2$, particularly with doses of *l*-AMPH which influence the NE system (<6 mg/kg). Determination of the ED_{50} for half maximal inhibition of the control level of rearing via linear regression analysis of the descending portion of each dose effect curve revealed a dose-dependent decrease in the ED_{50} with doses of 30 and 125 mg/kg $MgCl_2$ compared to 0 mg/kg (Table 1).

DISCUSSION

Analysis of data generated using apomorphine stereotypy and *l*-amphetamine motor activity as behavioral assays to measure DA and NE functions demonstrated that $MgCl_2$ dose dependently enhanced the potency of these drugs, and by inference, that $MgCl_2$ enhanced the activity of these neurotransmitters. The enhanced potency was shown by greater behavioral effects at certain drug doses, by shifts to the left in dose-response functions, and by decreases in the ED_{50} as dose of $MgCl_2$ increased. The most pronounced potency changes were measured in the sniffing and rearing responses. Because the behavioral measures of stereotypy and motor activity depend upon the central nervous system levels of NE and DA (16), the activity of these transmitters must be increased by the drugs in combination with the $MgCl_2$ in order to observe a more potent behavioral effect (5, 20, 27).

Herman and Brown (10) found that adenylate cyclase activity was dependent on the presence of divalent cations, Mg^{2+} being very effective in stimulating such activity. In a study by Williams *et al.* (32), it was shown that Mg^{2+} was an essential component of the reaction forming a high-affinity complex of agonist with receptor and was essential for full activation of adenylate cyclase by catecholamines. Several studies have shown the role of Mg^{2+} in enhancing the binding of NE and DA to their receptors (6, 9, 19, 26, 30, 31). Furthermore, the tyrosine hydroxylase enzyme is activated in the presence of Mg^{2+} (25). Buck *et al.* (2) permanently cannulated rats, fed them a low Mg^{2+} diet, and infused them with either 2 μg or 50 μg of Mg^{2+} in 80 μl of artificial cerebrospinal fluid. Monoamine analysis demonstrated relationship between the level of dopamine and concentration of Mg^{2+}, with a larger amount of DA in the brains of those rats receiving 50 μg Mg^{2+} than those receiving 2 μg Mg^{2+}. Thus, the present in vivo studies are consistent with some of the physiological effects of Mg^{2+} found in vitro which suggest that Mg^{2+} activates catecholamine systems.

Since it appears that increasing doses of $MgCl_2$ enhance DA and NE functions, the hypothesis that Mg^{2+} has stimulant properties is considerably strengthened. Doses of 30 and 125 mg/kg $MgCl_2$ have opposite influences on aggressive behavior, with the lower dose enhancing and the higher dose inhibiting that behavior (12). The stimulatory effects of low doses are probably related to stimulation of NE and DA systems, and the disruptive effects of high doses are probably related to the over-stimulation of NE and DA systems. In this regard, $MgCl_2$ is also like other psychomotor stimulants such as *d*-amphetamine and cocaine which are thought to produce their similar behavioral effects on aggression via similar neurotransmitter actions (21–23). Since $MgCl_2$ has also been shown to enhance the potency of cocaine and to attenuate the potency of haloperidol on mouse aggression (14), it would be of considerable interest to determine if $MgCl_2$ interacts with psychomotor stimulants on behaviors predictive of the abuse potential of drugs such as self-administration (7) and conditioned place preference (29).

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