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Stimulant-Like Effects of Magnesium on Aggression in Mice[1]

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IZENWASSER, S. E., K. GARCIA-VALDEZ AND K. M. KANTAK. *Stimulant-like effects of magnesium on aggression in mice.* PHARMACOL BIOCHEM BEHAV **25**(6) 1195–1199, 1986.—The effects of magnesium excesses resulting from daily injections of magnesium chloride ($MgCl_2$) were examined on offensive behavior in a resident-intruder situation. Male mice tested 5 min post-injection of 15 mg/kg or 30 mg/kg exhibited a significantly greater number of attacks and threats than saline controls; while in mice injected with 125 mg/kg threat and attack behaviors were decreased. No tolerance developed to this decrease which persisted throughout the 15 day injection period. Tolerance to the aggression enhancing effects developed in the 30 mg/kg group which returned to normal by Day 4 and in the 15 mg/kg group which returned to normal by Day 15. Two weeks following the last injection, all groups performed equally. When mice were tested prior to daily injections on Days 4, 8, and 15 in a second experiment, there were no $MgCl_2$ dose differences in threat or attack behavior, thus there was no cumulative effect of $MgCl_2$ on behavior. These data and our previous data showing that $MgCl_2$ deficiencies reduce offensive aggression suggest an inverted U-shape function to magnesium's influence on behavior. Since aggression has been linked to the neurotransmitters dopamine, norepinephrine, and serotonin, and magnesium has been shown to be an important cofactor in the activity of these neurotransmitters, it is possible that the effects seen here are related to changes in one or more of these systems.

Acute administration Aggression Chronic administration Magnesium Stimulant

MAGNESIUM (Mg^{2+}) is the fourth most abundant mineral in the brain, and is necessary as a cofactor for many enzymatic reactions as well as for the binding of several neurotransmitters to their receptors. These include the dopamine (DA) receptor [20], serotonin (5-HT) receptor [13], alpha-2 adrenergic receptor [17] and beta-adrenergic receptor [10]. Furthermore, Mg^{2+} can activate tyrosine hydroxylase [15] and tryptophan hydroxylase [1] in the rat brain. Because the tyrosine hydroxylase enzyme [21] and the tryptophan hydroxylase enzyme [2] are not fully saturated *in vivo*, it is possible to produce changes in the rate at which the brain synthesizes DA, norepinephrine (NE) and 5-HT with Mg^{2+}

There is evidence that the catecholamines and serotonin are important for the expression of aggression in animals [4]. For example, it has been shown that dietary loading of tyrosine in mice produces an increase in attacks by residents on intruders and that this increase is correlated with a rise in brain DA [19]. Similarly, a tryptophan deficiency in mice leads to a reduction in isolation-induced fighting which is related to a decrease in brain 5-HT [9]. Other agents such as d-amphetamine and L-dopa, which are known to activate catecholamine neurotransmitter systems, have also been shown to increase threat and attack behaviors in rats [11], when administered in low doses. At high doses, however, these agents lead to a decrease in aggressive behaviors, thereby producing an inverted U-shaped relationship between stimulant-like agents and offensive aggression.

Previous research has shown that the restriction of dietary magnesium to 15%, 25%, or 50% of the daily requirement reduces offensive aggression in male mice in a resident-intruder situation [7]. This reduction was concentration and time dependent with greater deficiencies leading to greater decreases in aggressive behavior. Also reported were decreases in DA and NE functioning as evidenced by a decline in apormorphine and l-amphetamine induced behaviors.

The purpose of the following experiments was to examine the effects of acute and chronic Mg^{2+} excesses on offensive aggression. Based on the finding that restricting dietary Mg^{2+} decreased aggressive behaviors and because of the ability of Mg^{2+} to increase biogenic amine activity, it was expected that a chronic Mg^{2+} excess would increase offensive aggression.

METHOD

Animals

Adult male and female pairs of CFW strain mice (42 days old) from Charles River Breeding Labs, Portage, MI, were housed as residents of individual home cages of 11.5×7×5

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TABLE 1

ACUTE AND CHRONIC EFFECTS OF $MgCl_2$

Dose	(n)	Baseline	Day 1	4	8	15	29
			Threats (frequency)				
Saline	(16)	42.6 ± 4.0	38.2 ± 4.2	33.8 ± 4.1	29.7 ± 3.6	20.8 ± 3.0	21.5 ± 2.9
15	(5)	52.8 ± 2.6	†63.6 ± 13.2	†62.4 ± 13.3	*47.8 ± 5.3	27.4 ± 8.8	34.0 ± 5.0
30	(8)	45.6 ± 6.9	*54.7 ± 11.8	33.1 ± 8.6	34.2 ± 7.3	31.0 ± 4.2	33.3 ± 6.3
60	(5)	50.0 ± 3.6	39.6 ± 6.6	28.0 ± 11.3	24.0 ± 5.9	22.6 ± 4.0	23.0 ± 3.5
125	(12)	40.4 ± 2.6	*22.0 ± 4.8	†14.2 ± 3.4	†10.6 ± 3.1	9.3 ± 2.5	21.0 ± 4.1
			Latency (seconds)				
Saline		45.8 ± 10.5	32.6 ± 10.4	14.3 ± 4.8	25.6 ± 8.4	40.6 ± 13.8	32.5 ± 7.1
15		27.2 ± 11.3	10.2 ± 5.3	18.6 ± 15.4	13.0 ± 10.2	71.6 ± 57.4	5.6 ± 4.8
30		23.0 ± 14.3	21.6 ± 14.1	39.1 ± 21.4	31.8 ± 25.1	5.6 ± 2.0	24.0 ± 7.5
60		108.4 ± 31.2	28.8 ± 17.9	72.0 ± 57.1	41.4 ± 26.8	49.8 ± 31.5	44.0 ± 23.4
125		54.8 ± 19.6	45.9 ± 24.5	73.8 ± 32.3	†161.7 ± 36.8	*121.4 ± 38.6	*107.1 ± 38.8
			Locomotion (% of Baseline seconds)				
Saline		37.1 ± 4.1	106 ± 10	101 ± 12	93 ± 14	78 ± 19	103 ± 13
15		†17.6 ± 2.1	126 ± 20	97 ± 21	108 ± 9	99 ± 13	98 ± 10
30		52.5 ± 8.3	114 ± 31	105 ± 28	61 ± 10	61 ± 22	†48 ± 10
60		†80.5 ± 1.5	109 ± 10	86 ± 19	96 ± 34	61 ± 5	112 ± 26
125		45.5 ± 5.7	*69 ± 13	*40 ± 7	*45 ± 8	47 ± 6	†47 ± 8
			Body Weight (% of Baseline grams)				
Saline		26.4 ± 0.9	101 ± 1	103 ± 2	107 ± 2	108 ± 4	116 ± 3
15		*24.8 ± 0.6	100 ± 0	100 ± 0	109 ± 2	*114 ± 2	†128 ± 5
30		†28.1 ± 1.2	102 ± 1	105 ± 1	106 ± 1	108 ± 1	115 ± 2
60		†28.4 ± 1.3	101 ± 3	104 ± 2	105 ± 2	108 ± 2	113 ± 4
125		†30.8 ± 1.6	99 ± 2	100 ± 1	*100 ± 1	*101 ± 2	111 ± 3

Values are mean ± S.E.M. The number of subjects per group are in parentheses. Measures were taken 5 min post-injection after baseline on days 1, 4, 8, and 15 of $MgCl_2$ treatment. Measures were again taken on day 29, two weeks after the last injection.

*$p<0.05$ compared to the saline group.

†$p<0.01$ compared to the saline group.

inch clear boxes. Male mice which served as intruders to these residences were group housed. All animals were housed 2 weeks prior to the first testing session. A continuous 12 hour light/dark cycle and constant temperature (80°F) were maintained. All resident and intruder mice had ad lib tap water and standard Purina Lab Chow, which contains 2 g of Mg^{2+} per kg of food, which is well above the minimum Mg^{2+} requirement for mice of 500 mg/kg of food (National Research Council Recommendation).

Procedure

Prior to Day 1 of the experiment, each male resident was tested 2 to 4 times to determine a baseline level of offensive aggression and to insure a stable level of behavior prior to drug administration. For each male, the resident female and pups, if any, were removed from the home cage and a male intruder was introduced into the cage. Testing lasted for 5 min after the first attack, with 5 min allowed as the maximum attack latency by the resident male. The frequency of sideways threat postures and biting attacks and duration of general locomotion (to check for potential debilitating effects of magnesium) were recorded.

After stable baseline levels were established, groups of mice received either 0 (isotonic saline), 15, 30, 60, 125, or 250 mg/kg of $MgCl_2$ ($MgCl_2 \cdot 6\ H_2O$ obtained from Fisher Scientific; doses expressed as anhydrous salt) which were administered subcutaneously on a daily basis for a period of 15 days. The $MgCl_2$ was dissolved in 10 ml of distilled water and given in an injection volume of 10 ml/kg body weight. Two experiments were conducted. In one experiment, aggression testing took place 5 minutes post-injection on Days 1, 4, 8, and 15. In the second experiment, injections were administered daily for 15 days, but animals were tested prior to the injection, except on Day 1 where they were tested 5 min after the injection. This experiment was conducted to determine if the repeated administration of $MgCl_2$ had any cumulative effect on behavior from day to day. The animals in both experiments were again tested on Day 29 (two weeks after the last $MgCl_2$ injection). There were between 5 and 16 animals per group.

Statistics

The number of threats and attacks, latency to the first attack, duration of locomotion, and body weight were eval-

TABLE 2

CUMULATIVE EFFECTS OF $MgCl_2$

Dose	(n)	Baseline	Day 1	4	8	15	29
			Attack (frequency)				
Saline	(5)	24.2 ± 6.5	20.8 ± 6.2	20.8 ± 3.2	30.6 ± 6.8	25.4 ± 6.3	17.4 ± 7.8
15	(5)	27.0 ± 5.0	*40.2 ± 10.4	30.0 ± 8.9	19.2 ± 4.1	19.0 ± 6.1	15.5 ± 4.5
30	(5)	22.8 ± 2.7	30.6 ± 4.5	32.6 ± 8.6	21.8 ± 4.3	22.8 ± 4.6	12.6 ± 4.8
60	(5)	20.6 ± 5.5	21.2 ± 3.2	22.0 ± 4.7	18.6 ± 7.4	18.8 ± 3.3	15.2 ± 1.8
125	(5)	21.8 ± 3.3	*8.6 ± 4.1	33.0 ± 11.4	18.8 ± 6.0	22.2 ± 4.2	13.0 ± 3.9
			Body Weight (% of Baseline grams)				
Saline		28.0 ± 0.3	99 ± 1	104 ± 1	104 ± 1	105 ± 1	108 ± 1
15		28.2 ± 0.6	102 ± 1	102 ± 1	106 ± 1	109 ± 2	†114 ± 1
30		25.8 ± 0.7	99 ± 2	101 ± 1	103 ± 1	105 ± 1	†117 ± 1
60		28.8 ± 0.4	99 ± 2	105 ± 3	102 ± 1	104 ± 2	110 ± 1
125		27.4 ± 0.2	102 ± 2	102 ± 3	104 ± 2	104 ± 3	110 ± 2

Values are mean ± S.E.M. The number of subjects per group are in parentheses. Measures were taken 5 min post-injection after baseline on day 1 and 24 hr post-injection on days 4, 8, and 15 of $MgCl_2$ treatment. Measures were again taken on day 29, two weeks after the last injection.

*$p<0.05$ compared to the saline group.

†$p<0.01$ compared to the saline group.

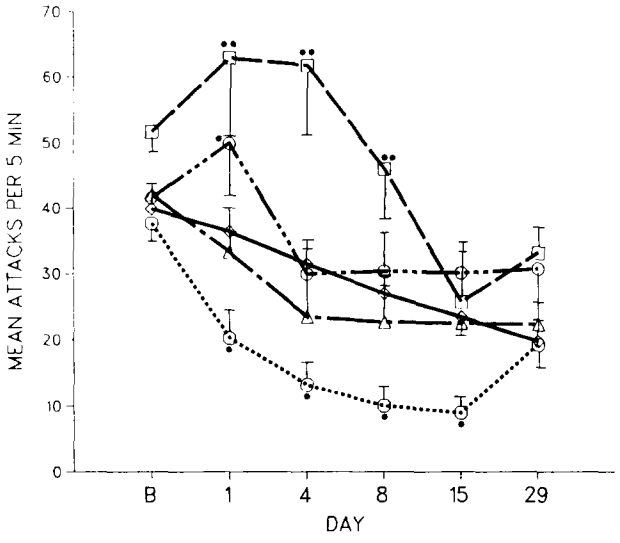

FIG. 1. Mean±S.E.M. Frequency of attacks per 5 min. Measures were taken 5 min post-injection on Days 1, 4, 8, and 15 of $MgCl_2$ treatment. Measures were again taken on Day 29, two weeks after the last injection. **$p<0.01$ and *$p<0.05$ compared to the saline control group. Octagon—125 mg/kg, triangle—60 mg/kg, circle—30 mg/kg, square—15 mg/kg, diamond—saline.

uated by 2-way analyses of variance with dose of $MgCl_2$ as one factor and day of injection the other repeated factor. Where applicable, the Duncan Multiple Range test was used for post-hoc testing.

RESULTS

Experiment 1: Acute and Chronic Effects of $MgCl_2$

Analysis of baseline frequencies of threats and attacks showed no differences across groups. On Day 1, the animals receiving 250 mg/kg $MgCl_2$ were completely sedated and therefore were unresponsive to the intruder. Subsequently, this dose was discontinued and was not included in any of the statistical tests.

Those mice receiving $MgCl_2$ showed dose-dependent changes in attack behavior as compared to saline controls following acute administration, $F(20,205)=2.16$, $p<0.0039$, with lower doses leading to increases and higher doses to decreases. As can be seen in Fig. 1, animals receiving either 15 ($p<0.01$) or 30 ($p<0.05$) mg/kg of $MgCl_2$ exhibited a significantly greater number of attacks on Day 1 than did saline controls, with 15 mg/kg producing a greater effect than 30 mg/kg. At the highest dose of 125 mg/kg, however, attack behavior was significantly decreased ($p<0.05$). The 60 mg/kg group exhibited control-like behavior and continued to do so through Day 29, which was 2 weeks following the last injection.

Chronically, the changes seen in the 15 mg/kg group persisted through Day 8 while those animals receiving 30 mg/kg returned to control levels by Day 4. In the 15 mg/kg group, the frequency of attack was less on Day 8 than on Days 1 and 4. The number of attacks mady by animals receiving 125 mg/kg remained significantly lower on all testing days during $MgCl_2$ administration. None of the groups differed from the saline controls on Day 29. Changes in the number of threats followed the same pattern and significance levels as that seen for attacks, $F(20,205)=2.03$, $p<0.0073$ (Table 1).

Latency to the first attack was significant for the dose by day interaction, $F(20,205)=1.99$, $p<0.0091$. There were no differences between groups in latency to the first attack during baseline or on Days 1 and 4 (Table 1). On Day 8, however, the group receiving 125 mg/kg $MgCl_2$ had significantly longer latencies than the saline controls ($p<0.01$). This difference diminished somewhat, although remained significantly different ($p<0.05$) through Days 15 and 29. These la-

tency differences were probably related to the fact that on Days 8, 15, and 29, several of resident mice in the 125 mg/kg $MgCl_2$ group failed to attack the intruder. This resulted in a maximum attack latency of 300 seconds for these animals.

Because the duration of locomotion was significantly different for some groups during baseline tests, these data were analyzed using percent of baseline for each group for Days 1 through 29. There were significant differences in duration of locomotion, $F(16,164)=2.49$, $p<0.0020$ (Table 1). Post-hoc analysis showed that the 125 mg/kg $MgCl_2$ group had significantly less locomotion than the saline group on Days 1, 4, 8, and 29 ($p<0.05$). By Day 15, the locomotion in the saline control group was significantly suppressed, but returned to baseline levels 2 weeks after the last injection. All other groups followed the same time course of changes as the saline control during the course of the injections. On Day 29, however, the 30 mg/kg group exhibited significantly less locomotion than the saline group ($p<0.01$).

Body weight across groups also differed significantly during baseline testing. Subsequently, these data were analyzed as percent of baseline. Overall, there were significant differences in percent of baseline body weights, $F(16,164)=2.12$, $p<0.0097$ (Table 1). No groups differed from the saline cotrol on Days 1 and 4. On Days 8 and 15, the 125 mg/kg $MgCl_2$ group had significantly lower weight gain than the saline group ($p<0.05$). On Days 15 and 29, the 15 mg/kg $MgCl_2$ group had a significantly higher weight gain than the saline group ($p<0.05$ and 0.01, respectively). The 30 and 60 mg/kg groups did not differ from the saline group on any days.

Experiment II: Cumulative Effects of $MgCl_2$

The overall analysis revealed significant differences in attack behavior, $F(20,95)=1.87$, $p<0.0238$. There were no differences across groups during baseline. On Day 1, when mice were tested 5 min post-injection, the 15 mg/kg group exhibited a significantly greater number of attacks than the saline controls ($p<0.05$). There was also an elevation in attacks in the 30 mg/kg groups on Day 1; this difference approached, but did not reach significance. A significant reduction in attacks was measured in the 125 mg/kg group compared to the saline group ($p<0.05$) on Day 1, while control-like behavior was observed in the 60 mg/kg group. These results essentially replicate those found in the first study. When mice were not injected prior to testing on Days 4, 8, and 15, there were no $MgCl_2$ dose differences in attack behavior, thus there was no cumulative effect of $MgCl_2$ on behavior.

Threat behavior followed the same pattern as attack behavior, $F(20,95)=1.91$, $p<0.0198$, with the 15 mg/kg $MgCl_2$ group having a greater number of threats on Day 1 ($p<0.05$) and the 125 mg/kg group having a smaller number of threats on Day 1 ($p<0.05$). There were no significant differences on any day for duration of locomotion or latency to first attack. Body weight was significantly affected by $MgCl_2$ treatment, $F(16,80)=2.82$, $p<0.0012$. These data were analyzed as percent of baseline (Table 2) and revealed that by Day 29, the 15 and 30 mg/kg $MgCl_2$ groups had significantly elevated body weights compared to the saline group ($p<0.01$). A reduced growth rate in the 125 mg/kg group was not observed in this study.

DISCUSSION

These data indicate that low doses of acutely administered $MgCl_2$ enhanced, while high doses inhibited, offensive aggression. The enhanced aggression was evidenced by an increase in threats and attacks, and the reduction in aggression was evidenced by a decrease in threats and attacks and an increase in latency to attack. The increased aggression following low doses was dose-dependent with 15 mg/kg producing a greater increase than 30 mg/kg. Following chronic administration, tolerance to the aggression enhancing effects developed when testing took place 5 min post-injection and occurred sooner with 30 mg/kg $MgCl_2$ than with 15 mg/kg. No tolerance developed, however, to the reduction in offensive aggression following a high dose (125 mg/kg) where aggressive behaviors remained suppressed throughout the injection period. Locomotion during the test session was fairly consistent in all groups, except in the 125 mg/kg group which had reductions in locomotion. Therefore, this dose of $MgCl_2$ influences both agonistic and nonagonistic behaviors. In Experiment 2, with testing taking place prior to the daily injection, there were no changes in offensive aggression after Day 1. Therefore, although there is a chronic effect, there is no cumulative effect of repeated daily injections. The development of tolerance can only be detected when an animal is injected and then tested with $MgCl_2$.

These data, together with the magnesium-deficiency data previously reported by this laboratory [7], demonstrate an inverted U-shaped relationship between Mg^{2+} and offensive aggression. Deficiencies and high excesses of Mg^{2+} inhibit offensive behaviors while moderate excesses enhance them. The findings that Mg^{2+} produces an inverted U-shaped function toward offensive aggression and produces tolerance at behavioral activating doses are highly suggestive that Mg^{2+} might have stimulant-like properties. Stimulants such as amphetamine and cocaine have been shown to have a similar effect, under appropriate conditions, on aggressive behaviors. Lower doses of these drugs increase aggression and higher doses reduce it [11,12]. Furthermore, higher doses of stimulants reduce both agonistic and nonagonistic behaviors. Tolerance develops to some of the behavioral effects of d-amphetamine and cocaine upon repeated administration, e.g., to licking [5] and locomotion [18]. However, a lack of tolerance to the aggression-inhibiting and locomotion-inhibiting effects of d-amphetamine has been demonstrated [14,18]. Since stimulants are known to activate the catecholamine systems and aggression has been linked to alterations in the neurotransmitters DA, NE and 5-HT [4], it is likely that the stimulant's effects on aggression are due to changes in one or more of these systems. The effects on aggression seen with Mg^{2+}, which is an important cofactor in the synthesis and binding of these neurotransmitters, are possibly related to increases in the activity of these monoamines because of the striking similarities on behavior between Mg^{2+} and stimulants. Some preliminary evidence from this laboratory indicates that this may be so, since it was demonstrated that Mg^{2+} shifts the dose response functions of apomorphine and l-amphetamine to the left [8].

Body weight was differentially affected by Mg^{2+}. A decrease in growth rate was observed in Experiment 1 with 125 mg/kg $MgCl_2$, which was an aggression reducing dose. In Experiment 2, however, this same dose, while still decreasing offensive aggression, had no effect on body weight. Therefore, the reduction in aggression is not dependent on a change in body weight. The slower growth rate with 125 mg/kg $MgCl_2$ in Experiment 1 may be related to the higher baseline body weight levels rather than to the Mg^{2+} treatment. A diminished weight gain would be expected under these conditions. In addition, a dose of $MgCl_2$ which

facilitated aggressive behavior has been observed to increase growth rate. In both Experiments 1 and 2, the 15 mg/kg $MgCl_2$ animals had an increased growth rate. The body weights of the 30 mg/kg $MgCl_2$ group were elevated only in Experiment 2. These changes may be related to lower baseline body weight levels rather than to the Mg^{2+} treatment. A higher weight gain would be expected under these conditions. Thus, body weight appears to covary in some cases with changes in aggression, but there does not seem to be a consistent relationship between the two variables. Therefore, the changes in aggressive behavior are independent of body weight changes.

These studies with Mg^{2+} excesses and deficiencies may contribute to understanding the neurobiological significance of Mg^{2+}. Since it is distributed throughout the brain [3], it is likely that it would have an influence on behavior. These studies support the notion that Mg^{2+} has a strong influence on brain catecholamines and as a result has behavioral effects similar to stimulant drugs. If this hypothesis is correct, then it is predicted that Mg^{2+} should alter the potency of stimulants and have reinforcing stimulus and discriminative stimulus properties as stimulants do [6,22]. It has been shown *in vitro* that when Mg^{2+} is present, d- and l-amphetamine form the most stable chelates with ATP, which is thought to indicate an enhanced ability for these drugs to bind and be effective [16]. We have previously shown that Mg^{2+} alters the potency of apomorphine and l-amphetamine. When Mg^{2+} is low, the potency is decreased [7] and when Mg^{2+} is high, the potency is increased [8]. These data establish a direct link between Mg^{2+} and stimulant drugs.

In conclusion, more studies need to be done to examine the stimulant nature of Mg^{2+}. This would have implications for the treatment of a variety of disorders thought to involve alterations in brain catecholamines. These include drug abuse and hyperactivity. If Mg^{2+} can increase the potency of catecholamine stimulating drugs, then smaller amounts of drugs would be needed. This might retard or reduce tolerance and dependence to that drug.

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