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Failure of Magnesium to Maintain Self-Administration in Cocaine-Naive Rats

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KANTAK, K. M., J. F. BOURG AND S. I. LAWLEY. *Failure of magnesium to maintain self-administration in cocaine-naive rats.* PHARMACOL BIOCHEM BEHAV **36**(1) 9–12, 1990.—Previous research has shown that magnesium interacts with cocaine in such a way that it potentiates its action in a variety of behavioral situations. More recently, it has been demonstrated that magnesium will dose dependently substitute for cocaine self-administration and reduce the intake of cocaine. It is of considerable interest to determine if magnesium would be self-administered in cocaine-naive animals. The results of two experiments demonstrate that magnesium is not self-administered by cocaine-naive rats since although responding for magnesium chloride is above hypertonic saline control levels on day 1 of access, this responding is not maintained on subsequent days, does not occur in a regularly spaced pattern over time, and is not inversely related to dose. Taken together these data indicate that magnesium is a substitute for cocaine that has low abuse potential.

Self-administration Cocaine Magnesium Drug abuse

STIMULANT effects of magnesium chloride ($MgCl_2$) have been shown following its administration in a variety of behavioral situations. These behaviors include mouse aggression (7–9), drug-induced stereotypy and motor activity (10), and conditioned place preference (13,14). It has recently been demonstrated that intravenous $MgCl_2$ will dose dependently substitute for cocaine on an FR1 schedule of reinforcement (11), and that subcutaneous $MgCl_2$ will dose dependently lower the rate of cocaine self-administration (12). Thus, in animals that are experienced with cocaine, $MgCl_2$ appears to increase its reinforcing action and cause animals to behave as if cocaine were available. Whether or not $MgCl_2$ is self-administered in cocaine-naive animals is an interesting question that emerges from this research. Such information would provide an index of the primary rewarding properties of $MgCl_2$ and its abuse potential.

METHOD

Subjects

Male Wistar rats (Charles River Breeding Labs, Wilmington, MA), weighing 250 g upon arrival, were individually housed in hanging stainless steel $10 \times 7 \times 7$ inch cages. Light (0800 hr on, 2000 hr off) and temperature ($74 \pm 4°C$) were automatically controlled. Rats had free access to tap water and Purina Lab Chow Blocks, except during experimental sessions when food was restricted to 16 g per day.

Each rat was surgically implanted with a jugular catheter (22) under pentobarbital anesthesia with halothane or brevital anesthesia as needed. The catheter was passed subcutaneously to the dorsal surface and attached to a stainless steel anchor button which was sutured to the back muscles of the rat. Stainless steel tubing, which emerged 1 cm from the teflon acorn nut top of the anchor button, was closed off with a crimped piece of teflon tubing. The outside skin was sutured over the anchor button, finishing with a purse string stitch around the center post of the anchor button. All rats were infused daily with 0.5 ml of 8.5 units/ml heparinized saline followed by 0.1 ml of 1000 units/ml heparinized saline.

Apparatus

Each of 4 Gerbrands Model A operant conditioning units was outfitted with a response lever, feeder, food cup and stimulus light and was enclosed in a lighted and ventilated sound attenuated cubicle. A spring leash, which protected the fluid line, passed from the dorsal surface of the rat through the top of the cage and was mounted to a fluid swivel. These were attached to a counter balanced arm to permit freedom of movement in each box. The design of the leash, swivel and balance arm was identical to that described by Smith *et al.* (19). The line from the swivel was connected to a Sage Instruments Single-Channel Syringe Pump which delivered precise volumes of drug. The pump was set at a rate of 0.57 ml/min and was outfitted with a 20 ml plastic syringe and 0.2 μm syringe filter. Experimental events were maintained by an AT compatible computer (Bit Bucket, Newton, MA) and an interface (Med Associates, East Fairfield, VT).

Training

Training for self-administration of $MgCl_2$ was carried out in a manner identical to training for cocaine self-administration (11). Initially, each rat was trained to lever press for 45 mg food pellets and was then given access to 100 pellets on an FR1 schedule. On the following day, each of 100 responses were reinforced with

food pellets. Beginning on the third test session, and continuing for the remainder of the experiment, rats were given 10-min access to food pellets or 100 pellets (which ever came first), before receiving a training dose of drug on an FR1 schedule for 3 hr. Each lever press for drug activated the infusion pump for the number of seconds needed to deliver a precise volume of drug that was required for the animal's weight for the specified drug dose (4). The stimulus light, which was not active during the pellet sessions, was illuminated for the duration of the infusion, and additional lever presses during an infusion had no consequences. The cocaine, $MgCl_2$ and 0.335 M NaCl (equal in molarity to the $MgCl_2$) were dissolved in 8.5 units of heparin per ml saline (for cocaine) or per ml distilled water (for $MgCl_2$ and NaCl). The cocaine HCl was in a concentration of 4 mg/ml, and the $MgCl_2$ was in a concentration of 32 mg/ml, expressed as the anhydrous concentration from $MgCl_2 \cdot 6H_2O$ (Fisher Scientific). These experimental conditions were those found to produce optimum performance in rats in acquiring a response for cocaine (11). For cocaine, acquisition takes only 1 to 2 days, it occurs in 100% of the rats tested, and animals readily discriminate the food component from the drug component which is cued by a white stimulus light. Responding for food is rapid with short interresponse intervals, and immediately after the first reinforcement with cocaine rather than food, responding pauses for 2 to 5 min and continues in this manner for the duration of the test session. By using pellet sessions, it is possible to determine if the rat is capable of lever pressing, if the lever pressing response is under the control of the drug, or if the lever pressing response is not under control of the drug. This last condition would engender food extinction responding where bursts of responding would be followed by long pauses and would indicate that the drug that is available is not reinforcing; whereas the preceding condition would engender regularly spaced responding throughout the test session which would indicate that the drug that is available is reinforcing.

Experimental Procedure

Two experiments were performed. In the first experiment, the acquisition of a response for different doses of $MgCl_2$ (1.5 mg/kg/infusion, n=3; 3 mg/kg/infusion, n=4; or 6 mg/kg/infusion, n=8) was examined and compared to acquisition responding for 0.75 mg/kg/infusion cocaine (n=4) and hypertonic NaCl (n=4). These doses were chosen because they were previously shown to substitute for self-administered cocaine (11). The number of responses and the time of occurrence for each response for individual animals was recorded over each 3 hr session for 5 days. From this information, the average responses/hr were calculated and individual event records were generated.

In a second experiment, 6 mg/kg/infusion $MgCl_2$ (n=3) was available as a training dose. After 5 days of access in 3 hr sessions, different doses of $MgCl_2$ (18, 12, 6 and 3 mg/kg/infusion) were substituted for the training dose over 4 days to determine if response frequency was inversely related to dose of $MgCl_2$. Average responses/hr were calculated and individual event records were generated.

RESULTS

Experiment 1: Acquisition of Responding for Different Doses of $MgCl_2$

Statistically, there was a significant interaction between the different acquisition drugs and day of access, $F(16,72)=1.9$, $p<0.03$. Acquisition of a response for 0.75 mg/kg/infusion cocaine proceeded as expected (Fig. 1a), with all animals showing a stable response (10 responses per hr) by day 2 of access. In

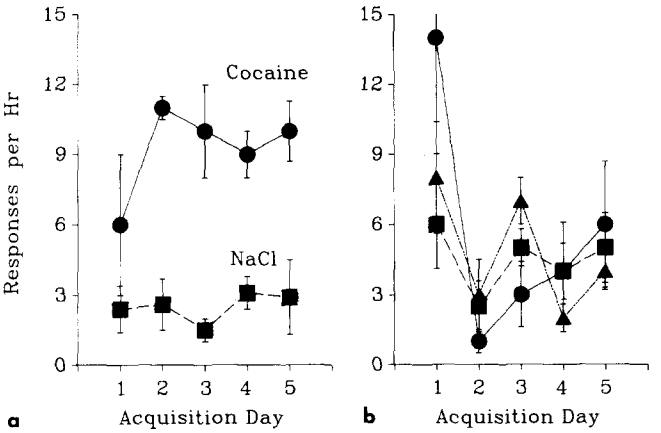

FIG. 1. Mean ± S.E.M. responses per hr during acquisition of a response for 0.75 mg/kg/infusion cocaine and 0.335 M NaCl (a) and for 1.5 (circles), 3.0 (squares), and 6.0 (triangles) mg/kg/infusion $MgCl_2$ (b).

animals given access to hypertonic NaCl (Fig. 1a), low levels of responding (2 responses per hr) were emitted on all 5 access days. These differences between cocaine and hypertonic NaCl were significant for each test day, $p<0.01$, except day 1 when cocaine responding was emitted at a rate of 6 responses per hr. Access to $MgCl_2$ in doses of 1.5 and 6 produced a level of responding that was significantly greater, $p<0.01$, than cocaine and hypertonic NaCl (12–14 responses per hr) on day 1 of access (Fig. 1b). On subsequent days, responding for the various doses of $MgCl_2$ were more than twice as great (4–6 responses per hr) as responding for hypertonic NaCl (2 responses per hr), but about half as great as responding for cocaine (10 responses per hr). The response rates for the $MgCl_2$ groups were below the rates for cocaine on days 2 and 3. These differences from cocaine were significant for the 1.5, 3 and 6 $MgCl_2$ doses on day 2, $p<0.01$, and for the 1.5 $MgCl_2$ dose on day 3, $p<0.05$. There were no differences between the $MgCl_2$ doses and cocaine on days 4 and 5. In addition, there were no differences in responding among the $MgCl_2$ doses, nor were any of the differences between NaCl and $MgCl_2$ significant on days 2 to 5. The distribution of responses on the event records show an evenly spaced pattern of responding on day 5 of cocaine availability (Fig. 2). In rats given access to hypertonic NaCl and the various doses of $MgCl_2$ (data is shown for the 6 mg/kg/infusion dose), the distribution of responses is not evenly spaced. The patterns show periodic bursts of responding which are characteristic of the absence of reinforcement.

Experiment 2: $MgCl_2$ Self-Administration Dose Response

In three animals that had access to 6 mg/kg/infusion $MgCl_2$ for 5 days (Fig. 3a), and whose number of responses was consistent from day to day (5 responses per hr), substitution of different doses of $MgCl_2$ maintained responding at about 3–5 responses per hr. This responding was not dose dependent (Fig. 3b).

DISCUSSION

A drug is considered to have primary reinforcing properties if it is self-administered, i.e., its administration will maintain lever pressing performance above control levels; if responding for the drug is inversely proportional to its dose; and if the pattern of intake is evenly spaced throughout a test session (18). The present results show that in cocaine-naive rats, $MgCl_2$ will only

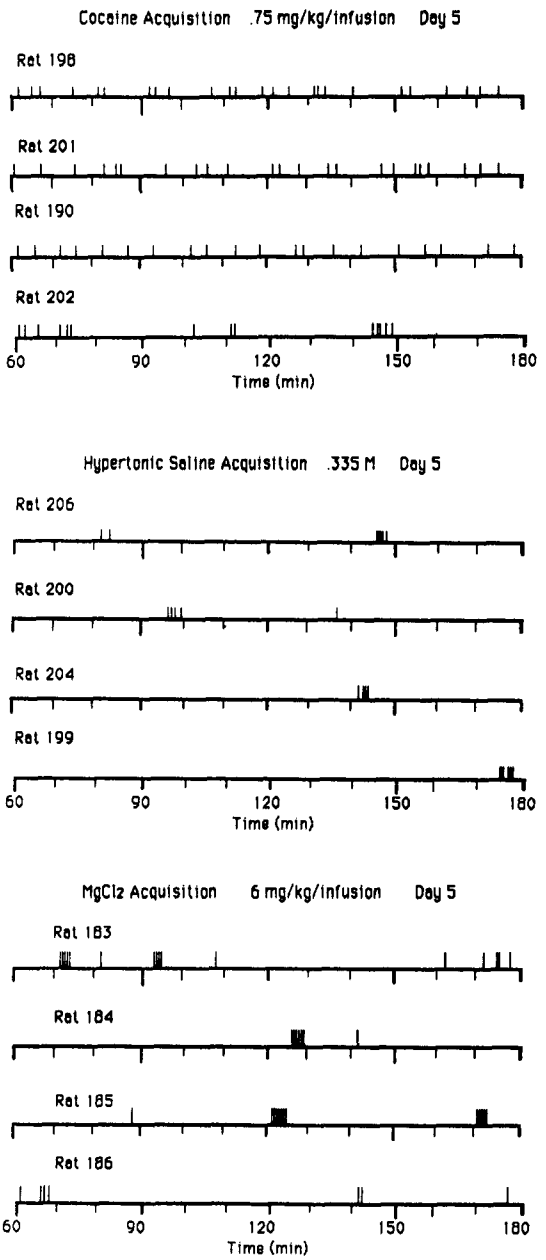

FIG. 2. Individual event records for the last two hr of the test session on day 5 of acquisition in groups receiving 0.75 mg/kg/infusion cocaine (top), 0.335 M NaCl (center), or 6 mg/kg/infusion $MgCl_2$ (bottom). Each upward deflection represents an infusion of the drug.

weakly maintain lever pressing performance above control levels, but this effect lasts for only 1 day, is not inversely proportional to dose, and is not characterized by an evenly spaced pattern of responding. The responding more resembles extinction of food reinforced responding because of the bursts followed by long pauses. The lack of a dose effect was observed when different doses were initially available to the rats (Experiment 1), and when they were available after access to a fixed training dose (Experiment 2). These data indicate that under the conditions of these experiments, $MgCl_2$ has no reinforcing ability in cocaine-naive rats.

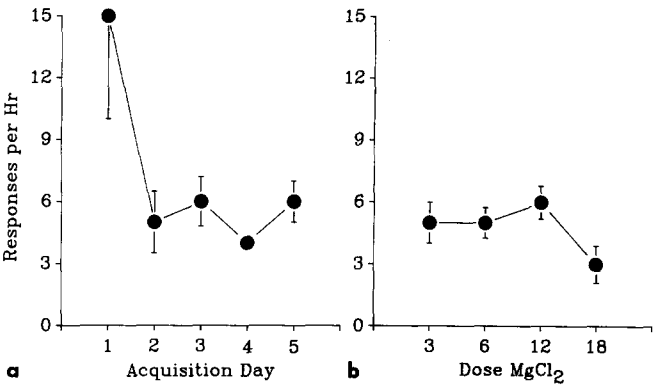

FIG. 3. Mean ± S.E.M. responses per hr during acquisition of a response for 6 mg/kg/infusion $MgCl_2$ (a) and following substitution with various doses of $MgCl_2$ (b).

These effects are in direct contrast to the robust substitution effects of $MgCl_2$ for cocaine (11). Substitution studies show that $MgCl_2$ maintains cocaine-like responding; it does so dose dependently to maintain a constant level of $MgCl_2$ intake; and it does so over a 10-day period of time both within and between sessions of cocaine access. Evenly spaced cocaine-like response patterns are also obtained. Furthermore, $MgCl_2$ reduces the self-administration of cocaine and lowers the intake of cocaine over days (12). It appears, therefore, that $MgCl_2$ can substitute for cocaine, but has low abuse potential due to its low primary reinforcing action.

It is not clear why $MgCl_2$ would potently substitute for the self-administration of cocaine, but not be self-administered in cocaine-naive animals. One possible explanation for these findings may be that the dopamine potentiating properties of Mg^{2+} (3, 6, 20, 21) are more pronounced in cocaine-treated rats because there are more dopamine receptors present. An increase in the number of D2 dopamine receptors occurs in the nucleus accumbens following chronic cocaine treatment (5). This enhanced sensitivity of D2 receptors in the reward pathway following cocaine may contribute to the ability of Mg^{2+} to be self-administered in cocaine-exposed animals.

An alternative explanation may be related to shared discriminative stimulus properties of cocaine and $MgCl_2$. A variety of psychomotor stimulant drugs generalize to the discriminative stimulus properties of cocaine (2), and thus these properties may contribute to their ability to substitute for cocaine in a self-administration situation. Recent conditioned place preference studies in mice (13,14) have shown that cocaine and $MgCl_2$ share stimulus properties. In animals that were conditioned to change place preference with cocaine, $MgCl_2$ consistently potentiated the cocaine shift when it was injected after conditioning had taken place using a cue reinstatement procedure where animals are injected and tested on the same day. In cocaine-naive mice, $MgCl_2$ had only a limited capacity to induce conditioned place preference, with 50% of the animals tested showing this effect. These effects are consistent with shared discriminative stimulus properties of cocaine and $MgCl_2$ because conditioned place preference procedures do not distinguish between the discriminative, interoceptive, and reinforcing stimulus properties of drugs when testing takes place on the same day as a drug injection (1). Thus, in the presence of cocaine, $MgCl_2$ might possess stimulus information that allows it to substitute for cocaine in a self-administration situation, but in the absence of cocaine, only limited discriminative and reinforcing stimulus information is present with $MgCl_2$ and hence self-administration does not occur.

Most drugs which have been shown to substitute for cocaine are also self-administered and are considered to have abuse potential. These include *d*-amphetamine (16), bromocriptine (24), methamphetamine (17), and methylphenidate (23). In this respect, $MgCl_2$ is different from other stimulant drugs because under an FR1 schedule of reinforcement, it substitutes for cocaine, but has low abuse potential. These types of effects on self-administration are considered ideal for pharmacotherapy of cocaine abusers (15).

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