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Central and Peripheral Minocycline Suppresses Motor Activity in Rats

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KOFMAN, O., S. VAN EMBDEN, C. ALPERT AND I. FUCHS. *Central and peripheral minocycline suppresses motor activity in rats.* PHARMACOL BIOCHEM BEHAV **44**(2) 397–402, 1993.—Minocycline (MIN) HCl is a tetracycline derivative previously shown to inhibit agonist-induced accumulation of cyclic adenosine monophosphate (cAMP) in vitro and suppress motor activity and amphetamine-induced hyperactivity in rats following SC injection. The present study examined the effect of IV and intracerebral MIN on baseline activity and amphetamine-induced hyperactivity. IV MIN suppressed both types of activity in doses of 100 and 150 mg/kg. When injected ICV, MIN (50 μg/2 μl) suppressed the increase in rearing elicited by amphetamine but did not affect baseline activity. MIN did not attenuate the behavioral suppression induced by the cAMP phosphodiesterase inhibitor rolipram. MIN apparently has centrally mediated effects on motor activity in rats; however, it is not yet possible to associate MIN's behavioral effects with its ability to inhibit agonist-induced stimulation of cAMP.

Minocycline Amphetamine Rolipram Hyperactivity Motor activity

THE hypothesis that an imbalance of neuronal cyclic adenosine monophosphate (cAMP) is involved in the etiology of bipolar affective disorder was suggested by the fact that lithium markedly inhibits agonist-stimulated increases in cAMP in laboratory animals, as well as in patients (9) and normal human subjects (9,10,26,38).

It has been suggested that this effect may be related to inhibition of agonist-stimulated G protein binding (1) or inhibition of the catalytic site of adenylate cyclase (24). Common side effects of lithium, such as polyuria, have also been attributed to inhibition of cAMP accumulation (6,14). Inhibition of agonist-stimulated cAMP is only one of several major biochemical effects of lithium, and it is not clear which of these effects underlies its therapeutic effects. One approach to this problem is to determine if drugs that share specific biochemical properties with lithium also have common behavioral effects.

Two tetracycline derivatives, demethylchlortetracycline (DMC) and minocycline (MIN), cause pronounced diuresis (13,28), which has been attributed to inhibition of antidiuretic hormone (ADH)-sensitive adenylate cyclase (7) distal to the ADH receptor (12), similar to the effects attributed to lithium (6,14,29). While the tetracyclines are rarely noted for their psychoactive properties (18,27,37), MIN was reported to cause lethargy, fatigue, vertigo, confusion, and disorientation in at least 25% of patients (8,11,15). Both DMC and MIN inhibited agonist-stimulated increases in cAMP in the rat cortex (22). Moreover, both drugs attenuated baseline and amphetamine-induced hyperactivity when injected acutely SC, but neither drug affected apomorphine-induced stereotypy. Chronic dietary DMC (0.4 and 0.8%) also attenuated amphetamine-induced hyperactivity (22). This behavioral profile is similar to that seen following lithium treatment in rats (23). Injections of tetracyclines IM or SC are known to be irritating; therefore, IV injection is usually preferred to prevent discomfort to patients (27). Because there was a possibility that SC injections of MIN in our previous study caused discomfort that might have partially contributed to the suppression of motor activity (22), the present study examined the effects of MIN administered both ICV and IV.

Because MIN inhibits agonist-stimulated increases in cAMP levels, the interaction between MIN and a cAMP-specific phosphodiesterase inhibitor, rolipram, was examined. Lithium has been shown to interact behaviorally with both the β-agonist clenbuterol (16) and with rolipram (31), reducing the hypoactivity produced by these drugs. Because clenbuterol and rolipram enhance cAMP levels (25,36), lithium's attenuation of the hypokinesia induced by these drugs may be related to its ability to suppress agonist-induced stimulation of cAMP. Consequently, it was postulated that MIN, which has similar effects on lithium in vitro (22), would attenuate rolipram-induced hypoactivity.

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EXPERIMENT 1: IV MINOCYCLINE REDUCES BASELINE ACTIVITY AND AMPHETAMINE-INDUCED HYPERACTIVITY

METHOD

Thirty-seven male Sprague-Dawley rats (180–280 g) were housed in groups of five with ad lib food and water, a reversed light/dark cycle, and a room temperature of 23°C. All experiments were run in the dark phase of the cycle, between 0800–1600 h. Rats were placed in the activity meter for 30 min 1 week prior to the experiment to habituate them to the cage.

Minocycline HCl (Lederle Laboratories, Pearl River, NY) (25, 100, or 150 mg/kg) or saline (0.9%) was injected in the tail vein. The saline solution was brought to pH 2.4, equal to that of the MIN solution. Thirty minutes after injection, rats were injected SC with either saline (0.9%) or amphetamine (1 mg/kg). All rats were tested for activity in an automated activity meter (Optovarimax, Columbus Instruments, Columbus, OH) for 15 min. Three photocells, placed 13 cm apart on two adjacent sides, measured ambulatory activity, and 15 vertical photocells, 3 cm apart, on each of two opposite sides recorded vertical activity (rearing). Total activity included the ambulatory activity score and the activity confined to a small space, that is, repeated crossing of a single photocell. Each animal was run twice, in both the saline (baseline) and amphetamine conditions. The order of sessions was counterbalanced (i.e., half received saline first and half received amphetamine first), and 1 week separated the two sessions. The combined data were analyzed by two-way analysis of variance (ANOVA), followed by posthoc Scheffé tests.

RESULTS

Amphetamine increased total activity, $F(1, 66) = 68.3$, $p < 0.00001$, ambulatory activity, $F(1, 64) = 86.5$, $p < 0.00001$, and vertical activity, $F(1, 66) = 24.7$, $p = 0.00005$. IV injections of MIN reduced all three measures of activity: total activity, $F(3, 66) = 6.96$, $p < 0.001$, ambulatory activity, $F(3, 64) = 5.03$, $p < 0.005$, and vertical activity, $F(3, 66) = 9.74$, $p < 0.0001$. There was no significant interaction between amphetamine and MIN, suggesting that MIN attenuated both baseline motor activity and amphetamine-induced hyperactivity (Fig. 1). Data points are missing for two subjects for ambulatory activity due to technical failure of the activity meter.

Posthoc Scheffé tests were conducted for the effect of each dose of MIN on the combined data from saline and amphetamine trials. The total activity and vertical activity were significantly suppressed by 100 mg/kg ($p < 0.01$) and 150 mg/kg MIN ($p < 0.005$). Ambulatory activity was significantly suppressed by 150 mg/kg MIN ($p < 0.02$), while the effect of 100 mg/kg approached statistical significance ($p = 0.05$).

EXPERIMENT 2: ICV MINOCYCLINE ATTENUATES AMPHETAMINE-INDUCED INCREASES IN REARING

METHOD

Thirty-two rats, randomly divided into 4 groups of 8, were implanted with cannulae (Plastic Products, Roanoke, VA) in the lateral ventricle using standard stereotaxic procedures under pentobarbital anesthesia (50 mg/kg). Coordinates for the cannula placement were 0.8 mm posterior to bregma, 1.4 mm lateral to bregma, and 5.0 mm below skull. Cannulae were fixed to jeweler's screws in the skull using dental acrylic. Following surgery, rats were injected with a nontetracycline antibiotic (Depomycin) and at least 1 week was allowed for recovery from surgery. Rats were housed individually in plastic cages with ad lib food and water.

Rats were injected SC with either isotonic saline or *d*-amphetamine (1 mg/kg) in a volume of 1 ml/kg and placed in their home cages for 5 min. Next, they were injected ICV with either 50 μg MIN HCl (pH 2.4) or 0.9% saline brought to pH 2.4. Injections were made manually with a Hamilton microsyringe (Hamilton Co., Reno, NV) in a volume of 2 μl over a period of 1 min. The injection cannula was left in place for 1 min following injection and then replaced by the dummy cannula. Immediately after ICV injection, rats were placed in an activity meter as described above and activity was recorded automatically during 30 min. Cannula placement was con-

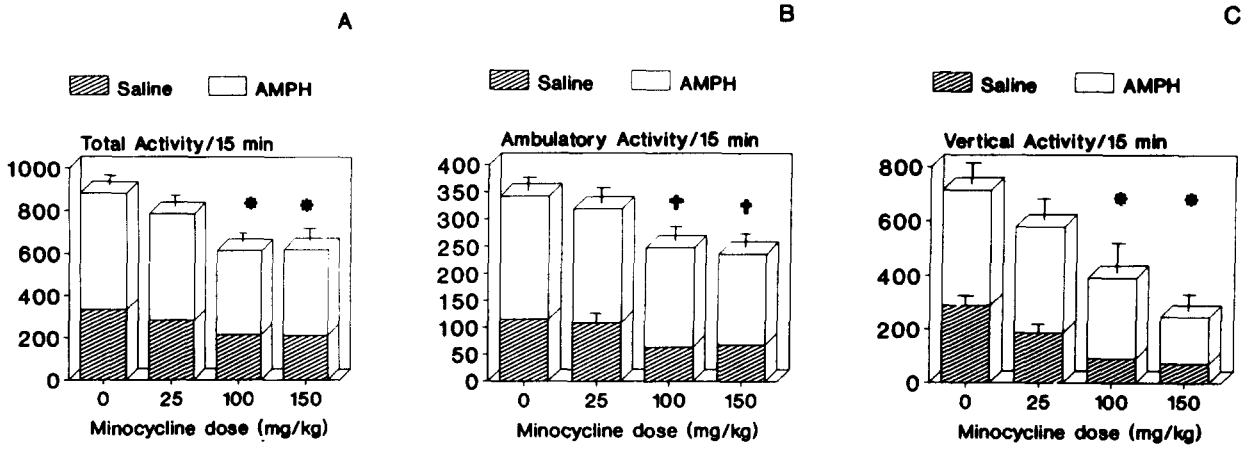

FIG. 1. Motor activity following IV injections of minocycline (MIN) (mean ± SEM). Rats were injected in the tail vein with vehicle or MIN (25, 100, or 150 mg/kg) and 0.5 h later with either saline (striped bars) or amphetamine (1 mg/kg) IP (open bars). Groups 0, 25, and 100 mg/kg MIN consist of 9 animals and the 150-mg/kg group of 10 animals. Rats were run under both saline and amphetamine conditions, and order of injection was counterbalanced. The ordinate represents the automatically measured activity during 15 min: total activity (A), ambulatory activity (B), and vertical activity (C). *$p < 0.01$; †$p < 0.05$ compared to control.

firmed by examining the cannula track in frozen brains. Two rats were excluded from analysis because of faulty cannula placements.

RESULTS

Two-way ANOVA showed that amphetamine significantly increased total activity, $F(1, 26) = 44.55$, $p = 0.00001$, ambulatory activity, $F(1, 26) = 32.54$, $p = 0.00004$, and vertical activity, $F(1, 26) = 19.11$, $p = 0.00035$. MIN had no effect on total activity and ambulatory activity, but significantly reduced vertical activity behavior, $F(1, 26) = 6.36$, $p < 0.02$. However, there was a significant interaction between MIN and amphetamine on rearing behavior, $F(1, 26) = 5.90$, $p = 0.02$, indicating that MIN was more effective in amphetamine-treated rats (Fig. 2). A test of simple main effects showed that amphetamine significantly increased activity for vehicle-injected rats, $F(1, 26) = 23.13$, $p < 0.001$, but not for rats that received MIN ICV, $F(1, 26) = 1.89$, ns.

EXPERIMENT 3: ICV MINOCYCLINE DOES NOT ATTENUATE ROLIPRAM-INDUCED HYPOKINESIA

METHOD

Forty-four rats were implanted with cannulae in the lateral ventricle as described above and injected ICV with either MIN (100 μg/2 μl) or saline brought to pH 2.4. The cannula was left in place for 1 min following injection and then replaced by the stylet. Immediately after ICV injection, rats were injected IP with rolipram (0.25 or 0.39 mg/kg) or vehicle (1.0% lactic acid in distilled water) and 5 min later placed in the activity monitor. Pilot studies indicated that suppression of behavior following rolipram was robust and long lasting. Because the 50-μg dose of MIN affected only rearing behavior in the previous experiment, a higher dose of MIN was tested in the present experiment. Activity was tested for 15 min as described above. Each rat was tested twice, using a crossover design, such that during the second session ICV and IP treatments were reversed, that is, rats that received rolipram in Session 1 (50% of subjects) received the IP vehicle in Session 2 and rats that received MIN in Session 1 (50% of subjects) received the ICV vehicle in Session 2. Because each rat was tested twice, the order of injection of MIN and rolipram was counterbalanced between Sessions 1 and 2 so that order of testing would not affect the behavioral measures. The data for each dose of rolipram were analyzed separately by two-way ANOVA.

RESULTS

Rolipram (0.39 mg/kg) significantly lowered total activity, $F(1, 41) = 40.93$, $p = 0.00001$, ambulatory activity, $F(1, 41) = 27.82$, $p = 0.00004$, and vertical activity, $F(1, 41) = 74.61$, $p < 0.00001$ (Fig. 3A). The lower dose of rolipram (0.25 mg/kg) lowered all three measures of activity as well: total activity, $F(1, 40) = 22.13$, $p = 0.00012$, ambulatory activity, $F(1, 40) = 19.03$, $p = 0.00023$, and vertical activity, $F(1, 40) = 44.13$, $p < 0.00001$. MIN did not affect the baseline behavior; nor was there a significant interaction between MIN and either dose of rolipram.

GENERAL DISCUSSION

The attenuation of motor activity following IV MIN corroborates a previous report that SC MIN suppressed both baseline activity and amphetamine-induced hyperactivity (22). These effects are more pronounced than the effects of lithium on an equivalent dose of amphetamine. Lithium effectively suppressed hyperactivity induced by a lower dose of amphetamine (0.5 mg/kg) but did not affect hyperactivity induced by higher doses (5,23). MIN can be given to humans in doses averaging 4–5 mg/kg, to a maximum of 34.3 mg/kg (15). The effective doses in this study (100–150 mg/kg, IV) ranged from 3–20 times the equivalent human dose.

When injected ICV, MIN affected motor behavior more selectively, that is, MIN suppressed amphetamine-induced increases in rearing but did not affect baseline motor activity. Rearing has been found to be more sensitive to the effects of lithium than other forms of locomotor activity (19,21). Although preliminary, these data suggest that the behavioral effects of MIN are centrally mediated. The similarity between the behavioral effects of MIN and those of lithium suggest that MIN or similar tetracycline derivatives may prove to be clinically beneficial antimanic drugs. Preliminary data showed

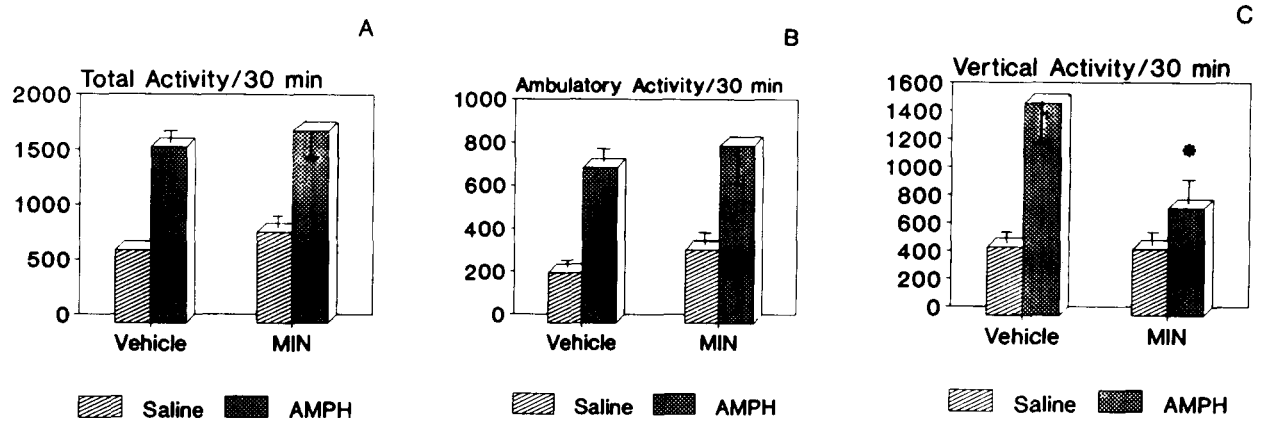

FIG. 2. Effects of ICV minocycline (MIN) (50 μg/2 μl) on total activity (A), ambulatory activity (B), and vertical activity (C) following SC saline or amphetamine (mean ± SEM). Amphetamine significantly increased rearing in vehicle- but not in MIN-treated rats. Vehicle-saline ($n = 8$), vehicle-amphetamine ($n = 7$), MIN-saline ($n = 8$), MIN-amphetamine ($n = 7$). The ordinate represents counts of vertical activity in 30 min. *$p < 0.001$ compared to control.

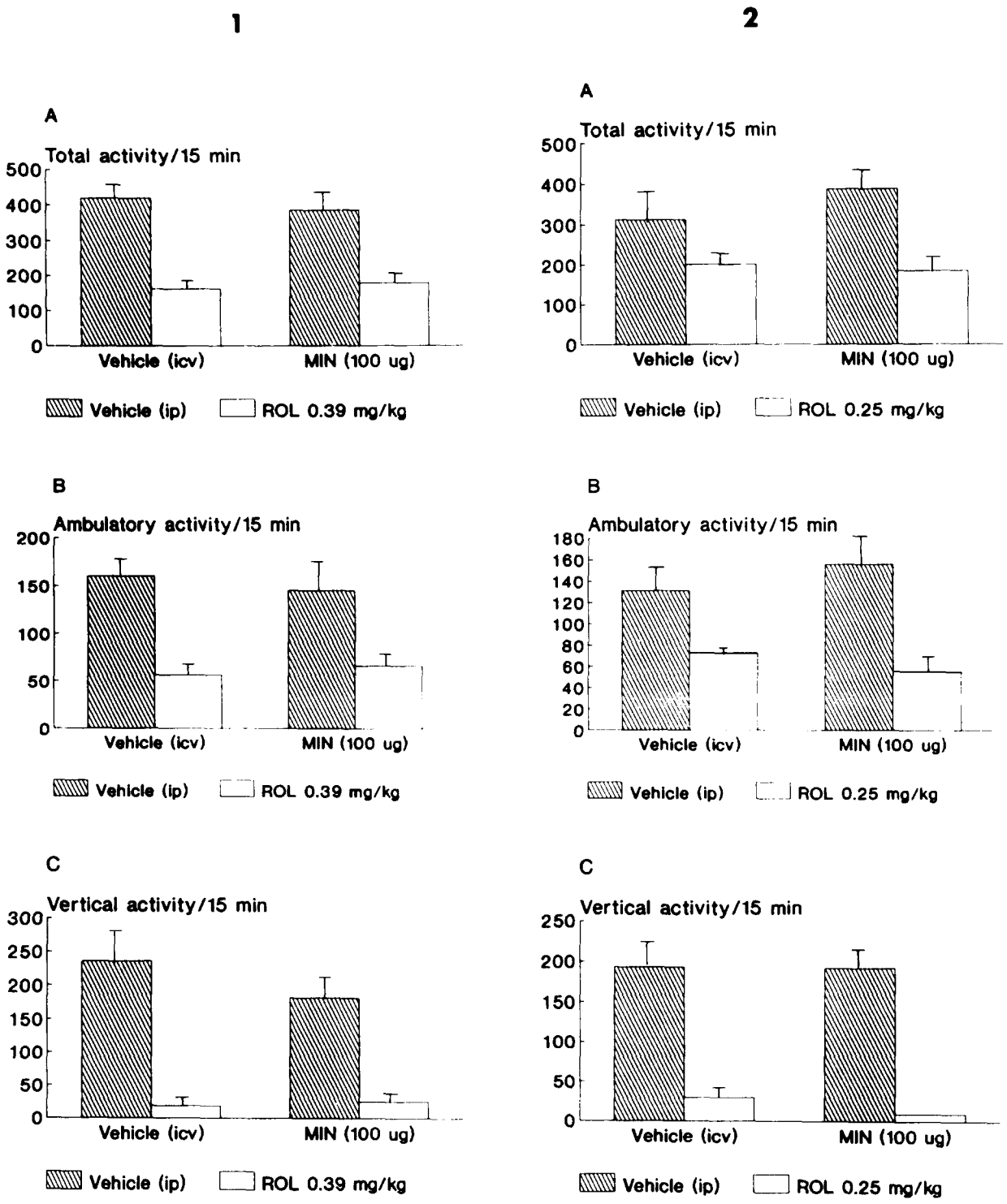

FIG. 3. Effects of ICV minocycline (MIN) (100 μg/2 μl) on hypokinesia induced by (−)rolipram (1) 0.39 mg/kg and (2) 0.25 mg/kg during 15 min (mean ± SEM). The ordinates for panels A–C are the same as in Fig. 1. The number of rats per group is as follows: (1)—vehicle-vehicle (9), vehicle-rolipram (13), MIN-vehicle (10), MIN-rolipram (13); (2)—vehicle-vehicle (12), vehicle-rolipram (10), MIN-vehicle (12), MIN-rolipram (10).

that a similar tetracycline, DMC, alleviated excited schizoaffective disorders in patients (5).

Central administration of MIN had a more specific effect than peripheral injections. Baseline active was not affected by either 50 or 100 μg MIN, and only elevated rearing behavior following amphetamine treatment was suppressed. Possibly, peripheral effects of the drug also contribute to the general depression of activity observed after IV injections; however, this issue can only be resolved after more comprehensive and comparative studies on the dose-response and time course of central and systemic injections of MIN.

The link beween MIN's ability to reduce agonist-stimulated elevations of cAMP (22) and its behavioral effects remains unresolved. We hypothesized that if MIN decreases cAMP levels it would counter the hypoactivity elicited by rolipram, an inhibitor of cAMP-specific phosphodiesterase that raises neuronal cAMP levels. Behavioral studies on drugs that alter cAMP levels suggest that increases in noradrenaline-sensitive cAMP are correlated with decreases in spontaneous locomotion in mice (17,32). Moreover, both forskolin and rolipram, which raise cAMP levels, decrease spontaneous activity in rodents (2,31,34–36).

Although stimulation of cAMP second messenger systems decreases spontaneous locomotion, drugs that lower cAMP, such as reserpine and lithium, reduce motor activity as well (4). One possible explanation for this phenomenon is the finding that cAMP levels are positively correlated with increases of motor activity in some brain regions and negatively correlated with activity in others (30). Despite the fact that drugs that enhance and drugs that diminish cAMP levels both have similar effects on *spontaneous* locomotion, several studies have shown that the hypoactivity induced by drugs that enhance cAMP levels, (e.g., clenbuterol or rolipram) can be attenuated by lithium (16,31) and, conversely, that rolipram can attenuate reserpine-induced hypokinesia (36). These data suggest that while hypoactivity per se is not an adequate model for clinical depression, drug-induced hypoactivity can be used to model pharmacological interactions between drugs that have opposing biochemical effects.

(−)Rolipram produced a profound depression of motor activity in this experiment at lower doses than previously reported (33–36). Rolipram-induced hypoactivity was not attenuated by MIN; however, the failure to observe a behavioral interaction between MIN and rolipram in this study could be attributed to the nonspecificity of rolipram. Rolipram was found to stimulate tyrosine hydroxylase and noradrenaline release (20), which may have contributed to its severe effect on motor activity.

In conclusion, the tetracycline derivative MIN suppresses motor activity and amphetamine-induced hyperactivity in rats. This effect appears to be centrally mediated and suggests that MIN has potential as an antimanic agent. However, it is not yet possible to relate the behavioral effects of MIN to its ability to inhibit agonist-induced increases in cAMP (22). The ability to decipher the mechanism of action for drugs that alleviate bipolar affective disorder is critical to the development of new drugs (3), which will be beneficial to patients who do not respond to lithium or cannot tolerate its side effects.

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