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A Comparison of the Motor-Activating Effects of Acute and Chronic Exposure to Amphetamine and Methylphenidate

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McNAMARA, C. G., E. S. DAVIDSON AND S. SCHENK. *A comparison of the motor-activating effects of acute and chronic exposure to amphetamine and methylphenidate.* PHARMACOL BIOCHEM BEHAV **45**(3) 729–732, 1993. – Acute exposure to methylphenidate (0.0, 5.0, 10.0, or 20.0 mg/kg) or amphetamine (0.0, 0.5, 1.0, 2.0, or 4.0 mg/kg) dose-dependently increased horizontal activity. The amphetamine-induced increase in activity was progressively augmented with repeated exposures over 7 days. In contrast, methylphenidate (20.0 mg/kg)-induced increases in activity became smaller with repeated exposures. Subthreshold doses of methylphenidate (1.0 or 5.0 mg/kg) were ineffective in stimulating motor activity even after 7 daily exposures. These findings suggest that, although sensitization develops with chronic amphetamine treatment, the consequence of chronic exposure to methylphenidate is tolerance. These data are discussed in terms of the different mechanisms through which methylphenidate and amphetamine affect central dopamine release.

Amphetamine Methylphenidate Sensitization Tolerance Dopamine Motor activity

SINCE it was first reported that amphetamine improved the symptoms of hyperactive and conduct-disordered children (4), psychostimulants have become standard treatment for children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). Most commonly, the stimulants *d*-amphetamine and methylphenidate HCl (Ritalin) are used, and both have been reported to be efficacious in the treatment of this disorder. Currently, methylphenidate (MPD) is the preferred treatment, since amphetamine's (AMPH) abuse potential has been recognized (10). It is estimated that about 3% of elementary-school-aged children are being treated with MPD for periods ranging from several months to several years (1). In spite of its widespread use, little is known about the long-term effects of MPD exposure.

MPD shares many behavioral effects with other psychostimulants, including AMPH. Both of these drugs stimulate motor activity (8) and can produce stereotypic responding in laboratory animals (7,26). AMPH is a potent reinforcer of operant behavior and has a demonstrated potential for abuse in the human population (10). MPD similarly has the potential to be a drug of abuse in humans (13), and some have reported that it is self-administered by primates (2,29). MPD substituted in a dose-dependent manner for AMPH in discrimination studies conducted with AMPH abusers (13). In addition, the reinforcing properties of MPD have been demonstrated in rats in tests of conditioned place preference (18).

With long-term intermittent exposure, the motor-stimulating effects of AMPH (17,19,28) and other stimulant drugs (21) become more pronounced. This reverse tolerance, or sensitization (22), has been correlated with an increased response of the mesolimbic dopamine system in response to the drug as measured by in vivo microdialysis (14,24). Chronic treatment with MPD also resulted in a sensitized stereotypic response in mice (27). However, in the human literature, there have been reports of tolerance to the benefits of long-term MPD treatment, in that the dose required to obtain the some effect must be increased over time (8,30). The absence of tolerance to chronic MPD has also been found (12,25). We are aware of no data concerning possible sensitization following MPD treatment in humans.

In an attempt to evaluate the consequences of long-term exposure to MPD, the present study examined the effects of intermittent exposures in tests of motor activity in laboratory rats. These effects were then compared to those of AMPH.

METHOD

Subjects

Male Sprague-Dawley rats (Harlan, TX) weighing 300–400 g were acclimated to the colony room for 1 week prior to testing. The animals were housed individually and allowed free access to food and water. The temperature-controlled

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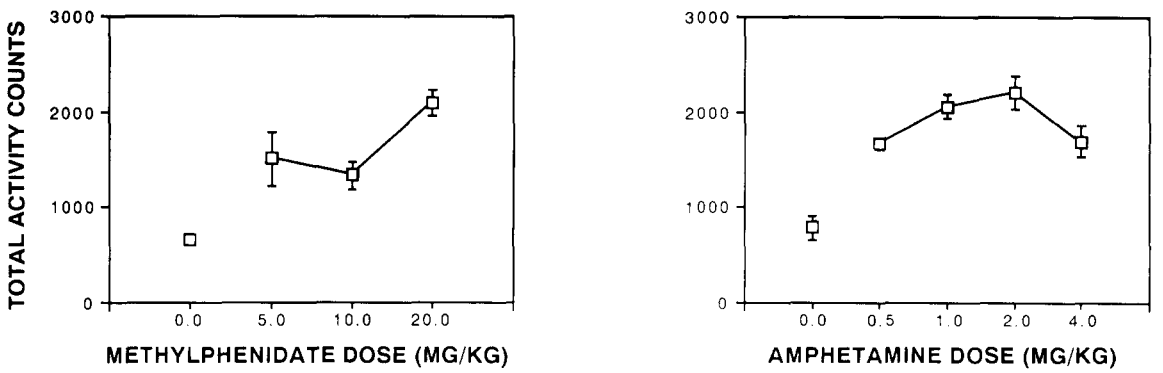

FIG. 1. Mean activity count totals (±SEM) of rats exposed to 0.0, 5.0, 10.0, or 20.0 mg/kg MPD (left panel), or 0.0, 0.5, 1.0, 2.0, or 4.0 mg/kg AMPH (right panel).

colony room was maintained on a 12L : 12D schedule, with light hours being between 0730 and 1930 h. Testing occurred during these times.

Apparatus

The activity chambers consisted of open-field boxes (38.1 × 38.1 × 38.1 cm) with grid floors. Each wall contained two photocells and receptors located 5.1 cm above the floor and 12.7 cm from each corner, which divided the field into nine equal spaces. Interruption of a beam was automatically recorded on a mechanical counter. Continual white noise masked other sources of noise. All testing was carried out in the dark.

Drugs

d-Amphetamine SO_4 was supplied by Sigma Chemical Co. (St. Louis, MO) and methylphenidate HCl was supplied by Research Biochemicals, Inc. (Natick, MA). All drug weights are based on the salt. Injection volume was 1.0 ml/kg.

EXPERIMENT 1—ACUTE ACTIVATING EFFECTS OF MPD AND AMPH

Procedure

To ascertain doses to be used in subsequent activity testing, an acute study was conducted using four doses of MPD and five doses of AMPH. Following an initial 30-min habituation period, rats were given an intraperitoneal injection of 0.0 (n = 6), 5.0 (n = 7), 10.0 (n = 8), or 20.0 (n = 7) mg/kg MPD dissolved in distilled water or 0.0 (n = 8), 0.5 (n = 8), 1.0 (n = 8), 2.0 (n = 8), or 4.0 (n = 8) mg/kg AMPH dissolved in physiological saline. Total activity was recorded for the 60-min postinjection period.

Results

Figure 1 shows the effects of MPD (left panel) and AMPH (right panel) on motor activity. The shapes of the dose-response curves for the two drugs are slightly different. The MPD function is fairly linear, with the largest dose (20.0 mg/kg) leading to the highest activity level. The AMPH curve is in the shape of an inverted U, with activity levels at 4.0 mg/kg being lower than those at 2.0 mg/kg. This is likely due to the introduction of stereotypic responding with the largest dose (4.0 mg/kg). For both drugs, the effects are dose dependent [MPD, $F(3, 24) = 10.097$, $p < 0.00020$; AMPH, $F(4, 35) = 20.411$, p ;0.0001]. Tukey post hoc analyses confirmed that activity levels for rats exposed to 5.0 and 20.0 mg/kg MPD were higher than activity levels of control rats ($p < 0.05$). Similarly, activity counts of rats given 0.5, 1.0, 2.0, or 4.0 mg/kg AMPH were significantly higher than activity counts of control rats.

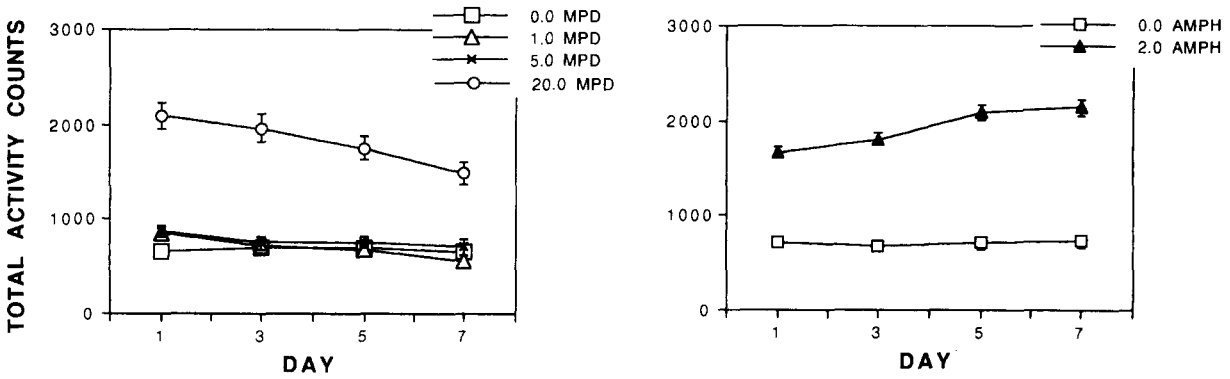

FIG. 2. Mean activity count totals (±SEM) on days 1, 3, 5, and 7 of rats exposed to 0.0, 1.0, 5.0, or 20.0 mg/kg MPD (left panel), or 0.0 or 2.0 mg/kg AMPH (right panel).

EXPERIMENT 2—CHRONIC EFFECTS OF MPD AND AMPH

Procedure

Rats were pretreated for 7 days with either the water vehicle (n = 22), 1.0 (n = 17), 5.0 (n = 17), or 20.0 (n = 22) mg/kg MPD. A second group was pretreated with either the saline vehicle (n = 20) or 2.0 (n = 25) mg/kg AMPH. The AMPH dose was chosen since it provided activity levels comparable to the highest dose of MPD (approx. 2000 counts in 60 min). They were injected daily in their home cages except on days 1, 3, 5, and 7. On these days, data were collected and injections were administered in the test cages. On test days, there was a 30-min preinjection habituation period. Activity data were collected for 60 min postinjection.

Results

Figure 2 (left panel) shows postinjection activity counts for vehicle- and MPD-exposed rats on days 1, 3, 5, and 7 of the treatment phase. The data from the 0.0-, 1.0-, and 5.0-mg/kg groups are clustered at about 800 counts across all days. A series of individual two-way ANOVAs (treatment × day) was conducted to compare the effects of each dose of MPD to the effects of the water vehicle. Although the 5.0-mg/kg dose increased activity in the acute study (Exp. 1), it failed to significantly increase activity in this second group, $F(1, 35) = 1.432$, $p > 0.05$. The 1.0-mg/kg dose also failed to significantly increase activity, $F(1, 35) = 0.122$, $p > 0.05$.

The highest dose of MPD (20.0 mg/kg) produced a substantial increase in activity, $F(1, 38) = 130.931$, $p < 0.0001$. There was also a significant interaction between treatment and days, $F(3, 114) = 4.461$, $p = 0.0053$. Simple effects analyses confirmed that the activity levels of rats exposed to 20.0 mg/kg MPD were greatest on day 1 and decreased with successive exposures, $F(3, 114) = 8.024$, $p < 0.001$. There was no significant change in the vehicle-exposed group over days ($p > 0.05$).

Figure 2 (right panel) shows postinjection activity counts for vehicle- and AMPH-exposed rats on days 1, 3, 5, and 7. A two-way ANOVA (treatment × day) of postinjection activity totals showed a significant interaction, $F(3, 126) = 5.814$, $p = 0.0009$. Simple effects analyses showed that the motor-activating effects of AMPH increased with each successive exposure, $F(3, 126) = 15.322$, $p < 0.0001$. The effect of saline exposure over days was not significant ($p > 0.05$).

DISCUSSION

The acute motor-activating effects of psychomotor stimulants are correlated with an increase in synaptic levels of dopamine (3). With chronic, intermittent exposure to low doses of AMPH, a sensitized behavioral and neurochemical response of the mesolimbic dopamine system occurs (23). Although the expression of the sensitized response is generally thought to be attributable to this neurochemical augmentation, the development of the behavioral sensitization may be due to changes that occur at the level of the dopamine cell bodies in the ventral tegmental area (15,16). Repeated injections of AMPH into the A10 or A9 dopamine cell body regions, but not into terminal areas, resulted in behavioral sensitization in response to systemically administered AMPH (16).

AMPH and MPD share the characteristic of facilitating release of dopamine and blocking reuptake (26), both of which increase synaptic levels of dopamine. The dose-dependent increases in activity produced by acute exposure to both AMPH and MPD could be a result of both of these neurochemical mechanisms.

Sensitization to the motor-activating effect of AMPH was produced by repeated injections. However, MPD produced an initial increase in activity that decreased with repeated exposures. The decrease could be attributed to increasing levels of stereotypy, which might be expected with higher doses of MPD, as has been found with other psychomotor stimulants (17,19,21). However, since we failed to observe successive increases in motor activity with repeated low-dose MPD treatment, it is unlikely that the rats were becoming sensitized. If so, subthreshold doses (1.0 and 5.0 mg/kg) should have become more effective as the rats become sensitized. Rather, the data are consistent with tolerance to this effect of the drug with repeated exposures.

The difference in the response to chronic exposures to these two stimulants may be due to differences in the effects of these drugs on somatodendritic dopamine release. AMPH is hypothesized to increase transmitter levels by enhancing release of newly synthesized unbound stores of dopamine sensitive to α-methyl-para-tyrosine (5). MPD is hypothesized to enhance release of granular stores that are sensitive to reserpine (8). Thus, only AMPH would be expected to release dopamine from cell body pools. If sensitization is due to a sequence of events initiated by stimulant-induced dopamine release from the cell body, then repeated AMPH, but not MPD, would be expected to result in sensitization.

On the other hand, tolerance with repeated exposure to MPD suggests that its impact at the level of the terminals may play a more critical role in these effects of long-term exposure. Indeed, in other behavioral tests, repeated AMPH and MPD exposures resulted in tolerance and cross-tolerance as opposed to sensitization (20). The mechanisms involved in the development of tolerance to chronic MPD may also be explained by the method by which this drug increases synaptic dopamine (i.e., by enhancing release of reserpine-sensitive granular storage pools). The newly synthesized agranular dopamine pool released by AMPH is characterized by a more rapid turnover rate, relative to the granular storage pool released by MPD (23). One hypothesis proposes that repeated intermittent exposure to AMPH results in larger, more readily releaseable pools of newly synthesized dopamine and diminished granular storage pools. There is the possibility that repeated exposure to MPD results in enhanced release of reserpine-sensitive storage pools, but due to the slower turnover rate, lowered levels of this pool of dopamine occurs. This hypothesis awaits confirmation with microdialysis studies.

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