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Psychostimulant-Induced Activity is Attenuated by Two Putative Dopamine Release Inhibitors

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CALCAGNETTI, D. J. AND M. D. SCHECHTER. *Psychostimulant-induced activity is attenuated by two putative dopamine release inhibitors.* PHARMACOL BIOCHEM BEHAV 43(4) 1023-1031, 1992.—Centrally administered amphetamine (AMPH), cathinone, (CATH), or cocaine (COC) have each been shown to produce elevated activity in rats and this effect is dose responsive. The question remains whether these psychostimulants share a common mechanism of action (i.e., do these psychostimulants act by releasing dopamine to increase activity levels?). Experiments were, therefore, conducted to measure the spontaneous activity of these three centrally administered psychostimulants in rats following pretreatment with two putative dopamine release inhibitors, viz., 5-(4-methyl-1 piperazinyl)imidazol(2,1-*b*) (1,3,5)-benzothiadiazepine maleate [CGS 10746B (CGS); 20 mg/kg)] and 4-(4-benzofurazanyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid methyl 1-methyl-ethyl ester [isradipine (ISR); 2.5 mg/kg)]. Rats fitted with chronic indwelling ventricular cannulae received a single dose of ICV-administered CATH (32 μg), AMPH (16 μg), COC (100 μg), or vehicle. Selection of these ICV doses of stimulant drugs was based upon results obtained in preliminary studies that indicated similar elevations of activity. ICV administration of each of these drugs/doses was preceded (20 min) by peripherally administered CGS, ISR, or vehicle. Results show that ICV CATH (32 μg), AMPH (16 μg), COC (100 μg) equieffectively elevate activity (two- to threefold) and that, in each case, this increase was significantly attenuated by pretreatment with CGS or ISR.

Dopamine Amphetamine Cathinone Cocaine Activity Isradipine CGS 10746B
Calcium channel blockade Intracerebroventricular Rats Antagonism

CONSUMING the juice extracted by chewing the young leaves of the Khat shrub (Catha edulis Forsk., family Celastraceae) produced effects that are practically indistinguishable from amphetamine (AMPH); these include euphoria, allayed fatigue, insomnia, and excitation [for review, see (23,30)]. (−)Cathinone (CATH) has been identified as the major psychoactive alkaloid contained in the Khat shrub (24). The activity-elevating effects of the other psychostimulants AMPH and cocaine (COC), as well as CATH, have been characterized following central administration in rats (3,4,8,19,25). Support for the hypothesis that psychostimulants require an intact dopaminergic system to exert their effects upon activity has been evidenced by reports that dopaminergic antagonists (21), or pretreatment with the relatively dopamine-selective neurotoxin 6-hydroxydopamine, into mesolimbic (i.e., nucleus accumbens) pathways significantly attenuates stimulant-induced activity (26). CATH and AMPH are believed to exert their effects by penetrating intraneural sites (18,22,23) to promote the presynaptic release of neural dopamine (27,44), whereas COC is believed to exert its effects primarily by binding to a site in the dopamine reuptake transporter (35) that, subsequently, results in reduced dopamine reuptake from the synapse (10,12). Thus, following administration of either CATH, AMPH, or COC the common end result is an increase in extracellular dopamine levels despite differing sites/mechanisms of action. The present series of experiments sought to compare the activity-elevating effects of doses of CATH, AMPH, and COC that were shown in pilot experiments to be approximately equieffective.

Putative dopamine release inhibitors were administered prior to psychostimulant injection to evidence the hypothesis that dopamine release is required for elevation of activity produced by psychostimulants. 5-(4-methyl-1 piperazinyl)imidazol(2,1-*b*)(1,3,5)-benzothiadiazepine maleate [CGS 10746B (CGS)] is an atypical antipsychotic of the benzothiadiazepine class that has been reported to inhibit dopamine release by mechanisms as yet unknown. However, CGS acts without interfering with dopamine metabolism or occupying dopamine

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receptors (1,2,45). In behavioral tests using the drug discrimination paradigm, peripherally administered CGS (10–40 mg/kg) attenuates CATH, AMPH, and COC discrimination (37,38). Using the place preference test, centrally administered CGS (15 μg) has been observed to block the rewarding effects of 32 μg CATH (unpublished observations). Therefore, one objective of the present studies was to test whether CGS would also attenuate CATH-, AMPH-, and COC-induced activity.

In addition to CGS, another dopamine release inhibitor was examined. It is hypothesized that calcium ion entry via voltage-dependent channels at neural cellular membranes plays a key role in neurotransmitter release (5,28,46). In vitro and in vivo evidence indicates that AMPH-stimulated dopamine release and synthesis is regulated, at least in part, by calcium (15,16,36,40). As CATH effects are nearly identical to AMPH (23), it would not be surprising if CATH's mechanism of action is also dependent upon the flow of calcium ions. In addition, there is evidence suggesting that COC effects involve neural calcium mechanisms, for example, Pani et al. (31) reported that the COC-induced increase in extracellular dopamine is attenuated by blockade of neural calcium channels of the L type (i.e., voltage-activated binding sites for 1,4-dihydropyridine blockers). 4-(4-benzofurazanyl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid methyl 1-methyl-ethyl ester [isradipine (ISR)] is a potent dihydropyridine calcium channel L-type blocker (9,11) and may act by interfering with the passage of calcium through these channels. Studies, using transstriatal dialysis to measure dopamine release, reveal that ISR (1–10 μM) stereoselectively and dose dependently produces a strong attenuation (40–75%) of BAY K8644-induced dopamine release (9). In addition, Pani et al. (32) reported that ISR (2.5 mg/kg) attenuates the elevated locomotor effects of peripherally injected COC (10 mg/kg) in rats. In light of these reports, a second objective of the present studies was to test whether ISR would attenuate any elevation of activity in rats following central administration of either CATH, AMPH, or COC. The rationale for the use of the ICV route for administration of the stimulants was to obviate any peripheral effects of the stimulants.

METHOD

Subjects

Male rats (purchased from Zivic-Miller Laboratories Inc., Allison Park, PA) of Sprague-Dawley descent served as subjects. Rats were individually housed in stainless steel hanging cages and allowed ad lib access to food (Purina 5008) and water. Housing took place in a colony room maintained at a constant temperature and humidity on a 12 L : 12 D cycle (dark onset at 1800 h). Activity measurements took place in a room separate from the colony room during the latter half of the light phase (1100–1600 h).

Surgery and Injection

Rats (425–590 g) were anesthetized using 100 mg/kg ketamine HCl plus a 0.15-ml injection of xylazine (10 mg/ml, Sigma Chemical Co., St. Louis, MO). A single stainless steel outer guide cannula (22 ga; Plastics One, Roanoke, VA) was stereotaxically implanted into the right lateral ventricle using the coordinates: 0.5 mm posterior to bregma, 1.5 mm lateral to midline, and 3.2 mm ventral to the surface of the dura, with the skull kept level between lambda and bregma (34). ICV injections were performed using a method modified from Myers (29). Drug solution was backloaded through a 28-ga internal cannula via a length of PE-20 tubing affixed to a 25-μl Hamilton microsyringe (Hamilton Co., Reno, NV) and administered in a total injection volume of 5.0 μl at a rate of 1.0 μl/4 s.

Drugs

(−)Cathinone HCl (NIDA, Rockville, MD), (−)cocaine HCl (Sigma), and (+)amphetamine sulfate (Sigma) were dissolved in sterile 0.9% saline. Saline served as the ICV vehicle (VEH) control injection. Peripheral injections of CGS (CIBA-GEIGY Corp., Summit, NJ) as well as ISR [(+)-PN 200-110, Sandoz Inc., East Hanover, NJ] were administered IP in an injection volume of 1 ml/kg. The dose of CGS (20 mg/kg) was selected on the basis of pilot data (unpublished observations). The dose of ISR (2.5 mg/kg) was selected on the basis of a study reporting dose–response and time course effects on locomotor behavior in rats (32). Reports of in vivo studies with CGS (1,2) and in vitro binding studies with ISR (41) indicate that CGS and ISR can penetrate the blood–brain barrier in rodents following IP injection. Saline served as the VEH control injection for CGS. ISR was dispersed ultrasonically in Tween-80 (9% solution in distilled water) as previously described (32). Tween-80 solution served as the VEH control for ISR. All drugs were prepared fresh on the day of use and all drug doses are expressed as the salt.

Apparatus and Procedure

Four pairs of infrared photosensors, affixed four per side in a 45.5 × 35.5 × 20.5-cm Plexiglas cage, were employed to measure activity. The sensors were situated 5.5 cm above the floor and 9.5 cm apart along the wall of the longer side as previously described (7). Each photosensor interruption resulted in one activity count that was automatically recorded by a computer in 5-min intervals throughout the 30- or 60-min testing sessions.

All subjects underwent thorough habituation consisting of daily handling and each spent 4 h per day in activity chambers on 3 days prior to the onset of data collection. This degree of habituation was instituted in an attempt to control for environmental novelty and allow for the establishment of stable baseline conditions.

Rats were tested with each drug a maximum of twice weekly. Drug day 1 treatment consisted of randomly assigning rats to one of two groups: Group 1 received an IP injection of the putative dopamine release inhibitor CGS or ISR and Group 2 received VEH. They were then placed into the activity cage for 20 min. At 20 min post-IP injection, rats were removed and received an ICV injection of one of the three stimulant drugs or their vehicle. Following completion of the ICV injection, rats were immediately returned to the activity cage and activity recording (for 1 h) was initiated. On drug day 2, IP treatments per group were counterbalanced, that is, the group that received IP VEH on day 1 received IP CGS or ISR on day 2. This design allowed each subject to act as its own control as well as to control for the possible effects of day of testing. Table 1 shows a complete summary of the drug/VEH administration order.

Statistical Analysis

Experiments were analyzed by one-factor analysis of variance (ANOVA) for differences across independent groups, that is, for comparison of ICV CATH + IP VEH, ICV AMPH + IP VEH, and ICV COC + IP VEH. Paired *t*-tests (42) were employed to test for differences between ICV stimu-

TABLE 1

SUMMARY OF STIMULANT DRUGS (32 μg CATH, 16 μg AMPH, OR 100 μg COC) AND/OR VEH ADMINISTRATION ORDER

Week	Drug Day 1	Drug Day 2
1		
Group 1	IP CGS (20 mg/kg) + ICV VEH⇒	IP VEH + ICV VEH
Group 2	IP vehicle + ICV VEH⇒	IP CGS + ICV VEH
2		
Group 1	IP CGS + ICV CATH (32 μg/rat)⇒	IP VEH + ICV CATH (32μg/rat)
Group 2	IP VEH + ICV CATH (32μg/rat)⇒	IP CGS + ICV CATH (32 μg/rat)
3		
Group 1	IP CGS + ICV AMPH (16 μg/rat)⇒	IP VEH + ICV AMPH (16 μg/rat)
Group 2	IP VEH + ICV AMPH (16μg/rat)⇒	IP CGS + ICV AMPH (16 μg/rat)
4		
Group 1	IP CGS + ICV COC (100μg/rat)⇒	IP VEH + ICV COC (100 μg/rat)
Group 2	IP VEH + ICV COC (100 μg/rat)⇒	IP CGS + ICV COC (100 μg/rat)

Rats (n = 11) received unilateral ICV injection of stimulant following IP injection of dopamine-release inhibitor CGS or VEH.

Note that in the second series of experiments peripheraly administered ISR (2.5 mg/kg; n = 8) was injected in place of CGS.

lant plus IP VEH treatment and ICV stimulant plus IP dopamine inhibitor treatments, as well as ICV CATH + IP VEH vs. ICV CATH + IP CGS. The level of significance was set at $p < 0.05$.

Histology

Subjects underwent histological verification of cannulae placements at the conclusion of activity testing. Following peripheral injection of sodium pentobarbital (200 mg/kg), rats were injected ICV with 4 μl Staedtler (C745) ink. Within 10 min following ink injection, each subject was perfused transcardially with physiological (0.9%) saline followed by a solution of buffered formalin (10%). Brains were rapidly removed from the cranial cavity and bathed in formalin. After 24 h, a freezing microtome was used to prepare coronal sections (40 μm thick) for visual verification of placements for lateral ventricular cannulae. Positive cannula placement was defined by the presence of ink throughout the ventricles. In the interval between the CGS and ISR experiments (conducted sequentially), three subjects were excluded from further testing when the cannulae bases in two subjects were loosened and one subject was found to be sick. Purging these subjects left 11 and 8 rats for experiments involving CGS and ISR, respectively.

RESULTS

Figure 1 (top) shows the mean (plus SEM) 1-h activity counts of rats receiving ICV-administered CATH, AMPH, and COC preceded by peripherally administered CGS or its VEH control injection. Figure 1 (bottom) depicts the mean (±SEM) 1-h activity of rats receiving ICV-administered CATH, AMPH, and COC with and without peripherally administered ISR or its VEH. One-way ANOVA of stimulant (CATH, AMPH, and COC) plus CGS treatment was nonsignificant, as was stimulant (CATH, AMPH, and COC) plus VEH treatment, $F(2, 32) < 2.4, p > 0.11$. These results demonstrate that, as shown in Fig. 1 (top), the stimulant groups displayed equieffective levels of activity and the activity of stimulant drug groups that received ISR also did not differ. The VEH-VEH and VEH-CGS treatment means did not differ and are displayed for comparative purposes. Comparisons of paired t-tests of stimulant drug plus VEH to stimulant drugs plus CGS treatment yielded significant differences for each of the three comparisons, $t(10) > 4.1, p < 0.002$.

Collectively, these results demonstrate that CGS significantly attenuated (by 60–80%) the activity-elevating effect of CATH, AMPH, and COC to levels approaching baseline activity. Figure 2 shows the mean (± SEM) time course activity counts of rats treated with ICV CATH, AMPH, and COC without and with CGS (20 mg/kg) pretreatment for comparative purposes.

Similar results were obtained in experiments with ISR pretreatment. One-way ANOVA of stimulant (CATH, AMPH, and COC) plus ISR treatment was nonsignificant, as was stimulant (CATH, AMPH, and COC) plus VEH treatment, $F(2, 23) < 0.7, p > 0.5$. These results again demonstrate that, as shown in Fig. 1 (bottom), the stimulant groups displayed equieffective levels of increased activity and the activity of stimulant drug groups that received ISR did not differ. The VEH-VEH and VEH-ISR treatment groups did not differ and their means are represented by the first two histogram bars. Paired t-test comparisons of stimulant dug plus VEH vs. stimulant drug plus ISR treatment yielded significant differences for each of the three comparisons, $t(7) > 2.6, p < 0.04$.

Like the CGS results, ISR significantly attenuated (by 33–56%) the activity-elevating effect of CATH, AMPH, and COC to levels approaching baseline activity. Figure 3 illustrates the mean (± SEM) time course activity counts of rats treated with ICV CATH, AMPH, and COC without and with ISR (2.5 mg/kg) pretreatment for comparative purposes. Although the activity count time course curves were not subjected to statistical analyses, but merely included for comparative purposes, it appears that the onset of each of the ICV-administered stimulant drugs was about 5–10 min and that this effect persisted for 30–40 min.

DISCUSSION

ICV injection of either CATH (32 μg), AMPH (16 μg), or COC (100 μg) produced roughly equivalent elevations of

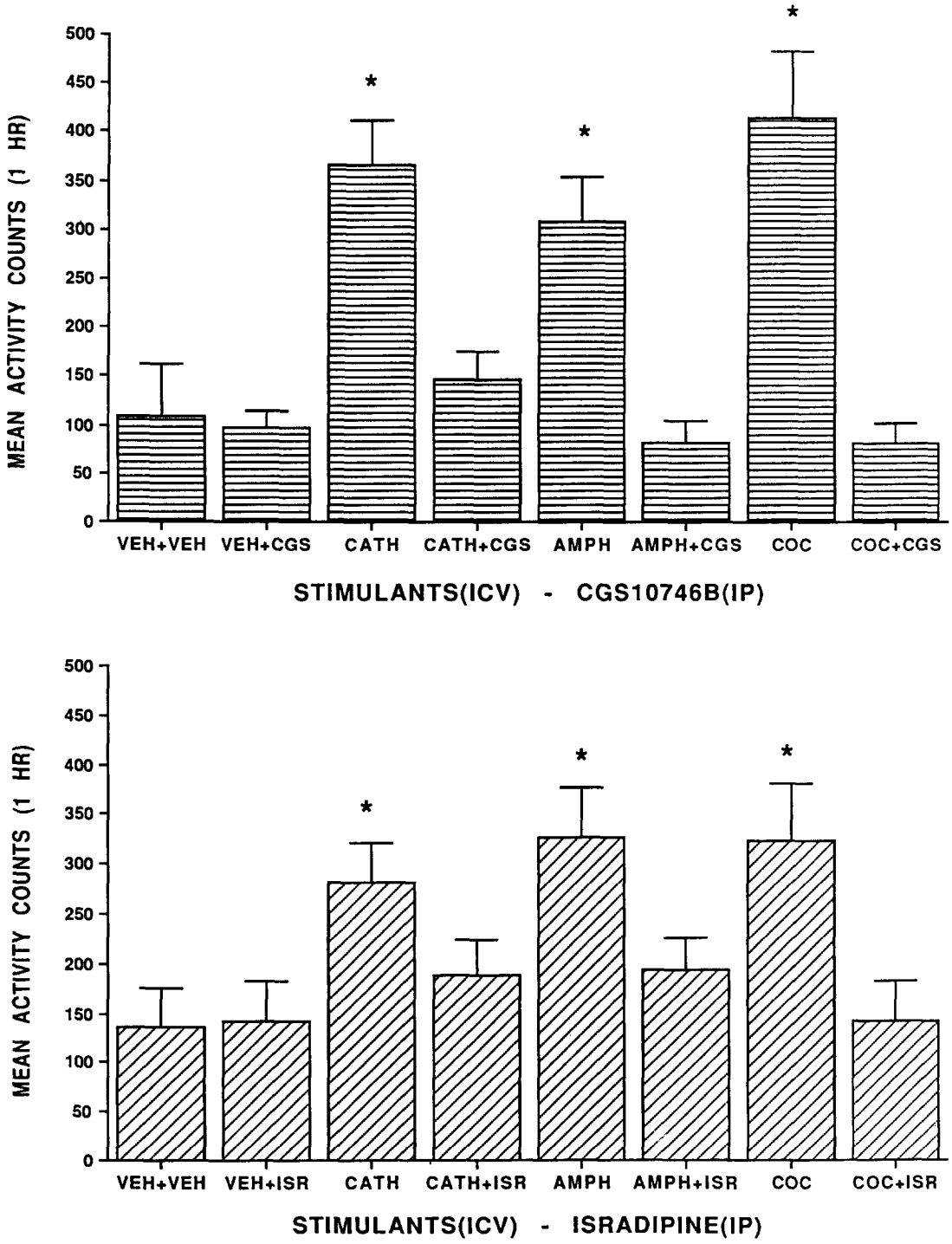

FIG. 1. Top: Mean (±SEM) 1-h total activity counts from rats (n = 11) receiving ICV-administered cathinone (CATH), amphetamine (AMPH), and cocaine (COC) with peripherally administered CGS 10746B (CGS) or vehicle (VEH) control injection. (Bottom): Mean (±SEM) 1-h total activity counts of rats (n = 8) receiving ICV-administered CATH, AMPH, and COC with peripherally administered isradipine (ISR) or VEH. *Significant ($p < 0.05$) differences of stimulant drug plus VEH vs. stimulant drug plus CGS (or ISR; bottom) using paired t-tests.

spontaneous activity as was suggested by pilot studies. The present result regarding ICV administration of COC stands in direct contrast to the finding that ICV administration of COC (10–100 μg/rat) did not elevate spontaneous activity (13); in fact, a trend toward a decrease in activity was suggested. The authors characterize their results as "puzzling" because they reported a significant elevation in activity following peripheral administration of COC. This discrepancy in results may be

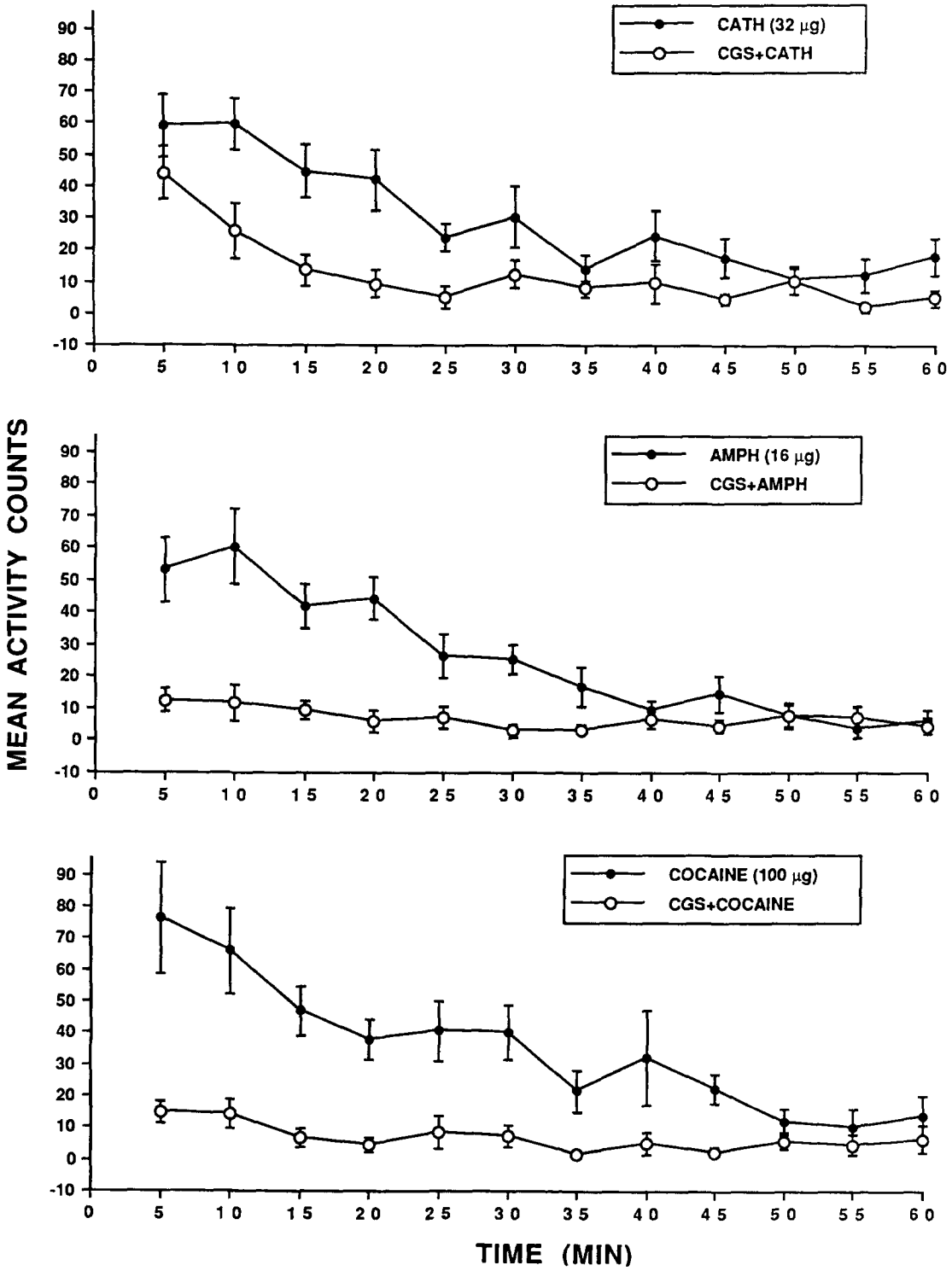

FIG. 2. Mean (± SEM) time course activity counts (per 5 min over a 1-h test session) of rats treated with ICV cathinone (CATH) (32 μg), amphetamine (AMPH) (16 μg), and cocaine (COC) (100 μg) without and with CGS 10746B (CGS) (20 mg/kg) pretreatment. These data are derived from a breakdown of data found in Fig. 1 (top).

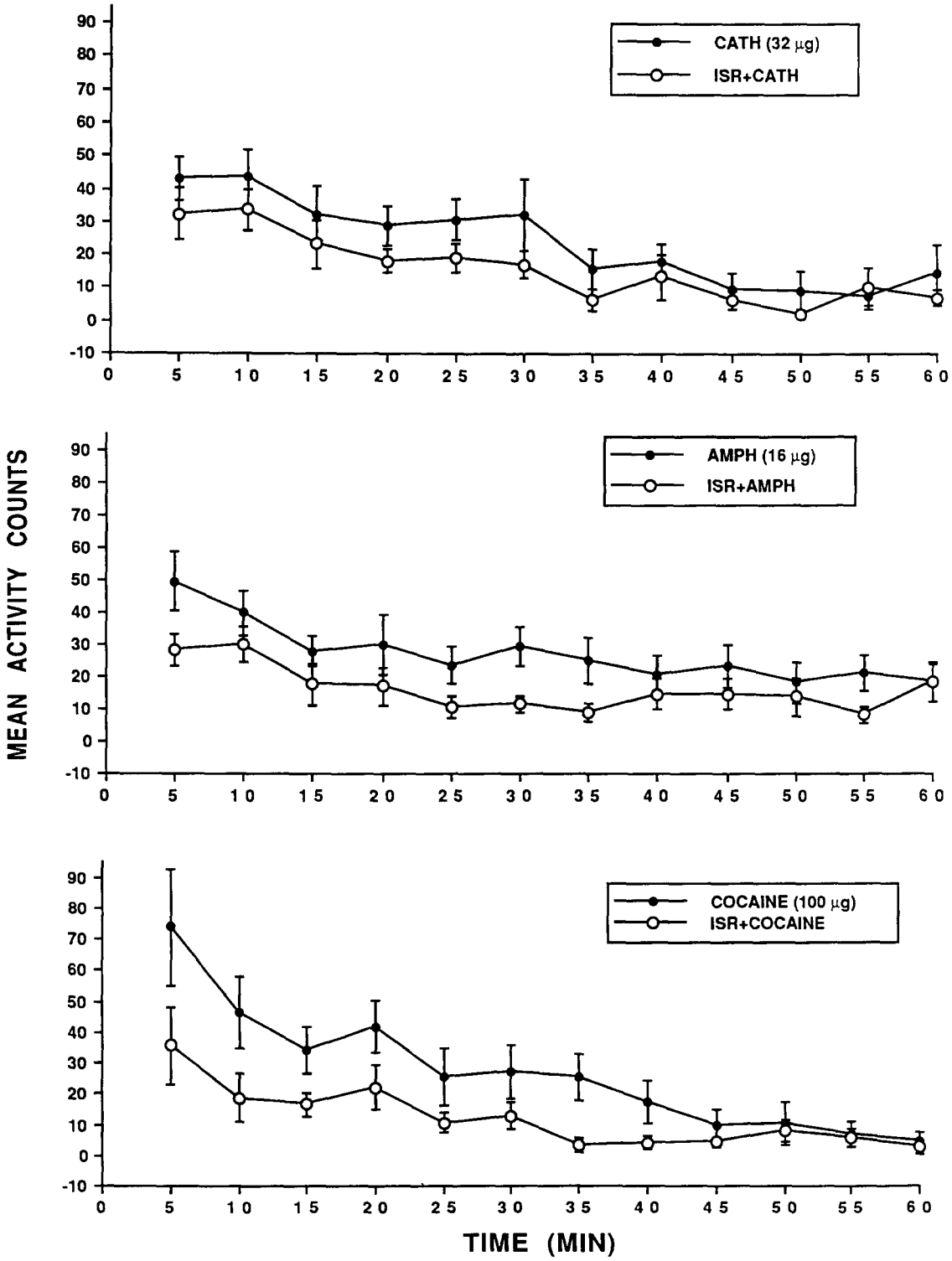

FIG. 3. Mean (± SEM) time course activity counts (per 5 min over a 1-h test session) of rats (n = 8) treated with ICV cathinone (CATH) (32 μg), amphetamine (AMPH) (16 μg), and cocaine (COC) (100 μg) without and with isradipine (ISR) (2.5 mg/kg) pretreatment. These data are derived from a breakdown of data found in Fig. 1 (bottom).

due to a peculiarity in the Fischer 344 rat strain that they used because recent evidence suggests that this strain is subsensitive to the activity-elevation effects of COC (17).

A behavioral indicator of dopamine mediation can be tested pharmacologically by using CGS because this agent decreases presynaptic release of dopamine (1,2) by mechanisms that neither block postsynaptic sites nor influence dopamine metabolism (such as might be seen with haloperidol or α-methylparatyrosine, respectively). In the drug discrimination paradigm, peripherally administered CGS (10–40 mg/kg) attenuates CATH and AMPH stimulus discrimination (38). The present series of experiments, therefore, set out to test whether dopamine release inhibitors would attenuate activity elevating effects of CATH, AMPH, and COC.

Inhibition of dopamine release may be accomplished in at least two ways: a) by reducing the firing frequency of the neuron via blockade of calcium ion channels necessary for cellular depolarization and/or b) by acting at intracellular sites in such a way as to inhibit the intracellular calcium-dependent sites for fusing of synaptic vesicles with the cellular membrane. Although additional evidence is necessary to identify the exact mechanism of CGS action, CGS presumably acts upon one of these sites/mechanisms to inhibit dopamine release. The present findings clearly show that pretreatment with CGS significantly attenuates the expression of elevated activity induced by either ICV-injected CATH, AMPH, or COC. In contrast, the activity measured after administration of CGS alone did not differ from baseline activity. This observation requires some attention because preliminary observations from this laboratory indicate that peripheral injection of CGS at doses above 2.5 mg/kg results in decreased activity (unpublished observations). There are two important differences that might explain these seemingly discordant findings. First, in the present study rats were habituated for several days to the testing room; second, when injected with CGS rats spent 20 min in the activity-measuring cages prior to stimulant injection. With the preliminary observations, rats had minimal habituation to the testing environment and once injected with CGS spent the 20-min pretreatment time in the home cage, and only then were they placed into the activity cages for the first time. These changes in procedure might serve to account for the lack of an observed decrease from baseline activity in the present experimentation.

Importantly, ISR did not affect baseline activity at the dose tested. This finding is in agreement with a report from another laboratory (32) that indicated that 2.5 mg/kg ISR does not attenuate baseline locomotor activity in rats. However, the effects of ISR and CGS on spontaneous baseline activity may be difficult to ascertain given the low levels of activity following habituation.

Pretreatment with ISR (2.5 mg/kg; 20 min) significantly attenuated the activity-elevating effects of ICV-administered CATH, AMPH, and COC. It may be hypothesized that ISR attenuates the effects of both CATH and AMPH for two reasons: First, there is ample evidence that AMPH-induced dopamine release is, at least in part, dependent upon a calcium mechanism (15,36,40); second, it has been demonstrated that ICV injection of 300 ng calcitonin, a peptide that selectively decreases blood calcium levels, potently attenuates AMPH-induced activity in rats (43). The present data represent the first evidence that ISR can attenuate the effects of centrally injected AMPH.

ISR also attenuated the activity-elevating effects of COC. Results from behavioral studies indicate that ISR is capable of attenuating the rewarding effect of peripherally injected COC (10 mg/kg) as seen in the conditioned place preference test (32). The attenuation of COC-induced place preference by ISR was dose related and did not produce sedation at doses ≤ 2.5 mg/kg. Another recent study reports that pretreatment with ISR dose-dependently increases the number of intravenous infusions of COC and morphine that rats will self-administer (14), indicating a cessation of reward. These findings may represent a significant research avenue in that it may be possible to regulate the rewarding effects of stimulant drugs by limiting Ca^{+2} movements across the plasma membrane via selective calcium channel blockade.

It appears that CGS attenuated stimulant-induced activity slightly more than did ISR. These observations stem from the slight rise in baseline during ISR testing, as well as from a slight decrease of the degree to which the stimulants elevated activity. The argument that tolerance to the stimulant effects occurred can be raised. However, this is unlikely for the following reasons. First, rats were only drug exposed for 2 days with 1 week or more interval between drug treatments. It is unlikely, given the acute nature of ICV injections, that significant tolerance had developed. Second, a substantial literature exists indicating that if any change in baseline responding does occur as a consequence of repeated stimulant drug exposure rats are observed to be *sensitized* to the stimulant drug effects (20,33,39). Clearly, no sensitization was observed. Another possible explanation might be that CGS treatment exerted some long-term residual carryover effects. Given this had occurred, ISR attenuation of stimulant-induced activity might be understated.

In summary, selected doses of CATH, AMPH, and COC produced equieffective elevation of activity following ICV administration. Pretreatment with CGS and ISR, two putative dopamine release inhibitors, attenuated the expression of these psychostimulant-induced increases in activity. These findings further evidence the role of dopaminergic mechanisms in the expression of locomotor activity and may suggest avenues to treat pathologic perturbations arising in neural dopamine systems as a consequence of abuse of each, or any, of these three psychostimulants. In this regard, a recent report indicated that in patients diagnosed with acute mania and symptoms of marked hyperactivity another dihydropyridine calcium channel blocker, nimodipine, showed promising results as a nonsedating alternative treatment to neuroleptics (6).

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