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Pharmacological Studies of the Acute Effects of (+)-3,4-Methylenedioxymethamphetamine on Locomotor Activity: Role of 5-$HT_{1B/1D}$ and 5-HT_2 Receptors

Michael G. Bankson, Ph.D., and Kathryn A. Cunningham, Ph.D.

The role of serotonin 5-HT_2 receptors (5-HT_2R) in the hyperactivity induced by (+)-3,4-methylenedioxymethamphetamine ((+)-MDMA; 3 mg/kg) was investigated. Hyperactivity induced by (+)-MDMA was robustly potentiated by the 5-$HT_{2B/2C}$R antagonist SB 206553 (1.0, 2.0, and 4.0 mg/kg). Administration of the 5-$HT_{1B/1D}$R antagonist GR 127935 (2.5 mg/kg) or the 5-HT_{2A}R antagonist M100907 (1.0 mg/kg) partially suppressed the potentiated hyperactivity seen following SB 206553 plus (+)-MDMA; a blockade to activity levels seen with (+)-MDMA alone was observed following the combination of GR 127935 plus M100907. A modest potentiative interaction was seen when SB 206553 was combined with the DA releaser amphetamine (0.5 mg/kg) or amphetamine plus the 5-HT releaser fenfluramine (4.0 mg/kg). SB 206553 (1–4 mg/kg), GR 127935 (2.5 mg/kg) and M100907 (1 mg/kg) did not alter spontaneous activity upon administration singly or in combination. These data suggest that activation of 5-HT_{2C}R exerts a strong inhibitory influence on the hyperactivity induced by (+)-MDMA, and that 5-HT_{2C}R blockade unmasks hyperactivity mediated through several mechanisms.
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KEY WORDS: *5-HT_{1B} receptors; 5-HT_{2A} receptors; 5-HT_{2C} receptors; M100907; MDL 100907; MDMA; 3,4-Methylenedioxymethamphetamine; SB 206553; Serotonin*

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a commonly abused amphetamine derivative that evokes a unique set of stimulant, emotional and perceptual effects distinguishable from the parent drug amphetamine (Greer and Tolbert 1986). The mechanisms of action of both amphetamine and MDMA are based upon their ability to reverse monoamine reuptake transporters resulting in monoamine release from nerve terminals (Rudnick and Wall 1992). Amphetamine is selective for the release of dopamine (DA) via the DA reuptake transporter (Crespi et al. 1997), while MDMA has greater affinity for the serotonin (5-hydroxytryptamine; 5-HT) transporter (SERT) (Battaglia et al. 1988; Crespi et al. 1997). The ratio of 5-HT release to DA release is much greater for MDMA than for amphetamine (Crespi et al. 1997), although MDMA, like amphetamine, does release a larger amount of DA than 5-HT (Gudelsky and Nash 1996; White et al. 1994; Yamamoto and Spanos 1988). There are also similarities and stark contrasts when comparing the overt behaviors expressed upon the administration of these two

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drugs. Both drugs increase locomotor activity in rodents, but amphetamine-induced activity is amplified throughout the activity monitor, while MDMA-induced activity occurs predominantly in the periphery of the chamber (Callaway et al. 1990; Gold et al. 1989; McCreary et al. 1999). MDMA also produces aspects of the "5-HT syndrome" (Spanos and Yamamoto 1989) and decreased investigatory behavior (Gold et al. 1989).

A large body of literature suggests that accumulation of DA in the synapse is a crucial mediator of the behavioral effects of psychostimulants such as amphetamine and cocaine (Kelly et al. 1975; Robledo et al. 1992). Dopamine antagonists (Kehne et al. 1996) and DA depletion with the DA neurotoxin 6-hydroxydopamine (Gold et al. 1989) have been noted to attenuate the behavioral effects of MDMA. However, several lines of evidence suggest that MDMA-induced activity is also critically dependent upon the release of 5-HT from terminals. For example, pretreatment with the 5-HT synthesis inhibitor *p*-chlorophenylalanine attenuated (+)-MDMA-induced hyperactivity (Callaway et al. 1990) while selective 5-HT reuptake inhibitors (SSRIs), which inhibit the binding of MDMA to the 5-HT transporter, blocked hyperactivity induced by (+)-MDMA, but not amphetamine (Callaway et al. 1990). Interestingly, when access to the SERT is blocked by an SSRI, the MDMA-evoked DA efflux in the striatum is greatly reduced (Gudelsky and Nash 1996; Koch and Galloway 1997). Furthermore, 5-HT has been shown to evoke receptor-dependent release of DA in the striatum (Nash 1990; Schmidt et al. 1994; Yamamoto et al. 1995) and, hence, 5-HT–induced DA release may mediate some of the unique effects of MDMA. The dual importance of both DA and 5-HT systems in mediating hyperactivity is unique to MDMA and suggests that the study of this amphetamine congener may provide insight into the interactive relationships between these two monoamine systems (see Bankson and Cunningham 2001).

The 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} receptors (5-HT_{1B}R, 5-HT_{2A}R and 5-HT_{2C}R) are localized to the nigrostriatal and mesocorticolimbic circuits (Barnes and Sharp 1999) implicated in locomotor activation, reward, and addictive behavior (Wise and Bozarth 1985). These receptors are also suggested to control DA function (Benloucif et al. 1993; Lucas and Spampinato 2000; Ng et al. 1999; Parsons et al. 1999) and are of especial interest in the behavioral effects of MDMA. Geyer and colleagues were the first to show that the spatial pattern of (+)-MDMA-induced activity is similar to that observed following administration of 5-$HT_{1B/1D}$R agonists (Callaway et al. 1992; Rempel et al. 1993). Non-selective 5-HT_1R antagonists were also shown to block hypermotility elicited by (+)-MDMA (Callaway et al. 1992). More recently, the selective 5-$HT_{1B/1D}$R antagonist GR 127935 has been shown to block (+)-MDMA-induced hyperactivity in rats to the level of saline controls (McCreary et al. 1999). These findings, coupled with the lack of effect of the selective 5-HT_{1A}R antagonist WAY 100635 (McCreary et al. 1999), suggest that stimulation of the 5-HT_{1B}R is a necessary condition for the expression of this behavioral effect of (+)-MDMA.

The hyperactivity induced by a high dose (20 mg/kg) of (±)-MDMA is attenuated by non-selective 5-HT_2R antagonists (e.g., ritanserin) and the selective 5-HT_{2A}R antagonist M100907 (Kehne et al. 1996). In contrast, the non-selective 5-$HT_{2/1}$R antagonist methysergide greatly enhanced the hyperactive effects of MDMA (Gold and Koob 1989). These paradoxical findings suggest that stimulation of 5-HT_{1B}R and 5-HT_{2A}R may contribute to the expression of MDMA-induced hyperactivity. The activation of 5-HT_{2C}R, which is thought to mediate the hypoactivity elicited by the direct 5-HT_{2C}R agonist *m*-chlorophenylpiperazine (MCPP) (Gleason and Shannon 1998; Heisler and Tecott 2000), may self-limit this behavior.

The aim of the present study was to test the hypothesis that activation of 5-HT_{2C}R self-limits the locomotor stimulation induced by a low dose (3 mg/kg) of (+)-MDMA in rats (McCreary et al. 1999; Paulus and Geyer 1992). To test this hypothesis, the selective 5-$HT_{2B/2C}$R antagonist SB 206553 was employed based upon its ability to discriminate between 5-HT_{2C}R (pK_i=7.92) and 5-HT_{2A}R (pK_i=5.8) without affinity for DA D_2, D_3 or D_4 receptors expressed in human HEK 293 cells (pK_i < 5; Kennett et al. 1996). The comparative ability of SB 206553 to potentiate the behavioral effects of the DA releaser amphetamine alone or in combination with the

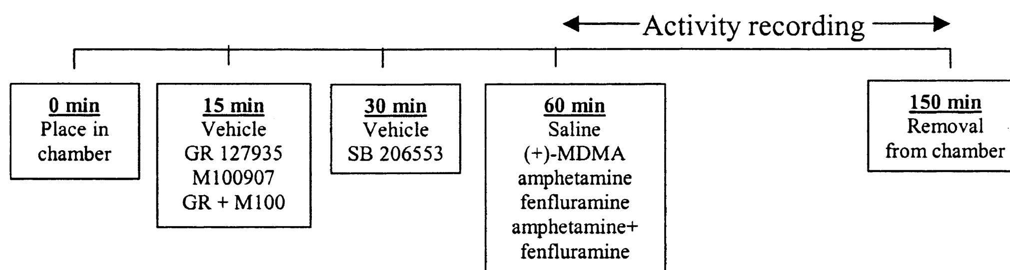

Figure 1. Time of treatment injections relative to automated recording of activity on test days.

selective 5-HT releaser fenfluramine was assessed to allow inference concerning the potential components of action of MDMA which might contribute to its observed effects. To further define the nature of the potentiation of MDMA-induced hyperactivity caused by SB 206553, GR 127935 and M100907 were utilized at doses previously shown to block $5\text{-HT}_{1B/1D}$R (Gobert et al. 1997; O'Neill et al. 1996) and 5-HT_{2A}R in vivo, respectively (Kehne et al. 1996; Sorensen et al. 1993); these are also doses of these drugs with which we have experience (McCreary and Cunningham 1999; McCreary et al. 1999; McMahon and Cunningham 2001a; 2001b).

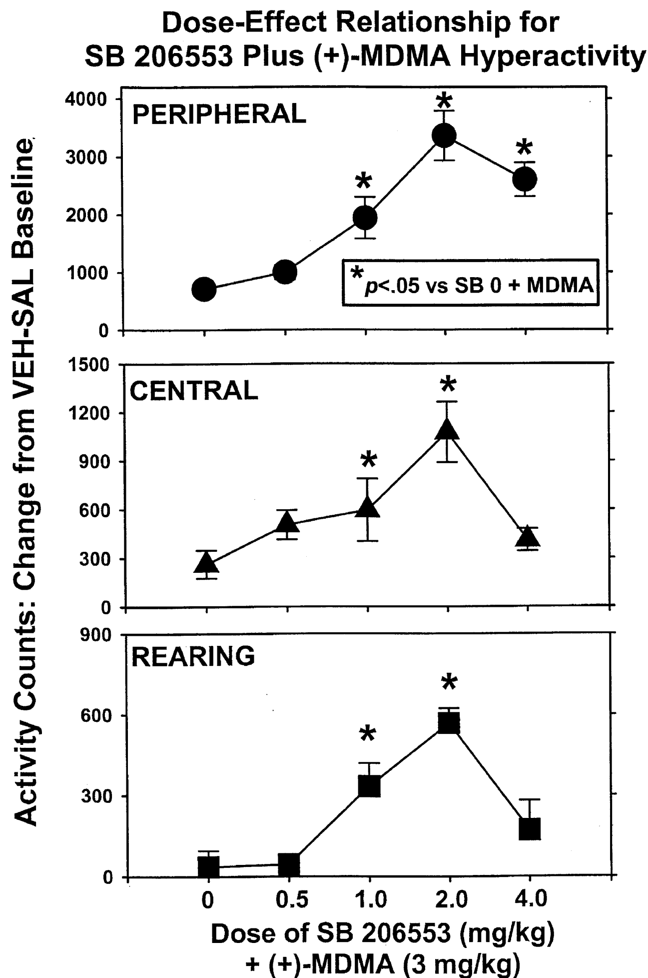

Figure 2. Dose-effect relationship for SB 206553 plus (+)-MDMA hyperactivity. Separate groups of rats (n = 8/group) were injected with SB 206553 (0.5-4 mg/kg i.p.) or β-cyclodextrin vehicle (1 ml/kg i.p.) followed 30 min later by injection of (+)-MDMA (3 mg/kg s.c.) or saline (1 ml/kg s.c.) (see Methods). Recording of activity began immediately in 5-min time periods and lasted for 90 min. Data are presented as mean change from vehicle-saline baseline over the 90-min test period (± SEM); see Statistical Analysis for further explanation. Peripheral, central, and rearing activity are shown in the top, middle, and bottom panels, respectively. The asterisks (*) denote activity levels that differed significantly from those of vehicle (+)-MDMA rats within a given activity measure.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) weighing 225–250g at the beginning of experimental procedures were housed in groups of four in a temperature (21–23°C) and humidity (40–50%) controlled environment for at least one week prior to experiments. Food and water were available ad libitum, except during experimental sessions. Lighting was maintained under a 12-h light-dark cycle (lights on 7:00 A.M.–7:00 P.M.). All experimental procedures were performed between 8:00 A.M. and 3:30 P.M. and were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Apparatus

Locomotor activity was quantified using a modified open field activity system under low light conditions (San Diego Instruments, San Diego, CA) housed within sound attenuated chambers. Each enclosure consisted of a clear Plexiglas open field (40 × 40 × 40 cm). A 4 × 4 photobeam matrix was located 4 cm above the cage floor with beams spaced at 8-cm intervals on the x and y planes. Another horizontal row of 16 photobeams located 16 cm from the floor surface provided each chamber with a measure of rearing activity. Interruptions of the photobeams resulted in counts of activity in the peripheral and central fields of the chamber. Activity recorded in the inner 16 × 16 cm of the open field was counted as central activity while the field bounded by the outer 12 cm band registered peripheral activity. Separate counts of peripheral and central activity were made by the control software (Photobeam Activity Software, San Diego Instruments) and stored for subsequent statistical evaluation. Video cameras located above the chambers were used to monitor activity continuously without disruption of behavior.

Behavioral Procedures

All rats were maintained in the colony room for a minimum of one week prior to behavioral testing for acclimation to daily handling procedures. Rats were habituated to the test chambers for 3 h per day on the two days prior to the start of the experiment. On the day of test, rats (n = 8/group) were placed in the activity monitors for 15 or 30 min prior to injections (Figure 1). Recording of activity in 5-min time epochs began immediately after the last injection and continued for 90

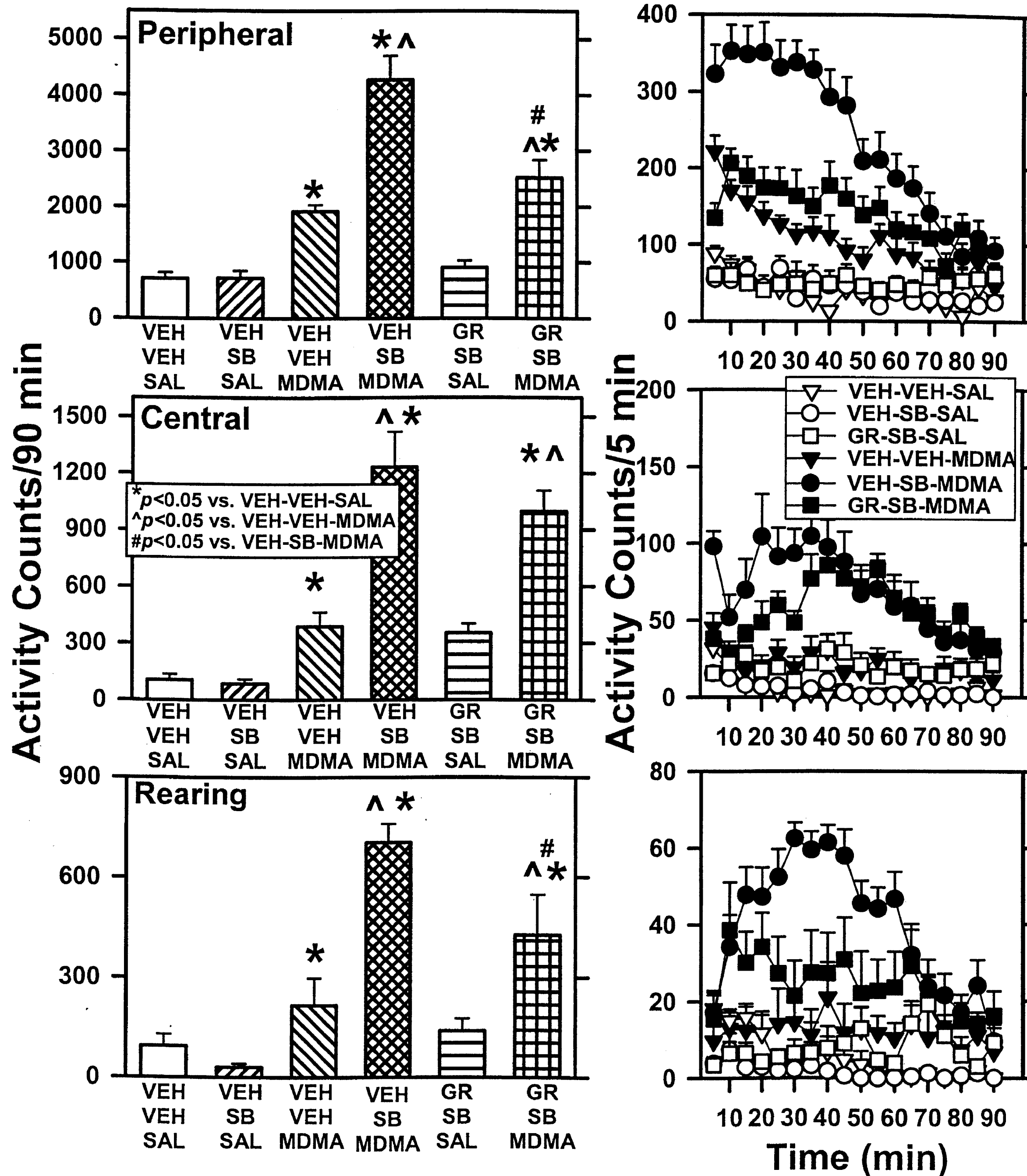

Figure 3. Effects of GR 127935 on SB 206553 plus (+)-MDMA hyperactivity. A group of rats ($n = 8$) was injected with GR 127935 (GR; 2.5 mg/kg i.p.) or β-cyclodextrin vehicle (VEH; 1 ml/kg i.p.) followed 15 min later by SB 206553 (SB; 2.0 mg/kg i.p.) or vehicle, and 30 min later with (+)-MDMA (MDMA; 3 mg/kg s.c.) or saline (SAL; 1 ml/kg s.c.). Recording of activity began immediately in 5-min time periods and lasted for 90 min. Left panels: The mean activity counts (± SEM) summed over the 90 min period beginning immediately after the final injection (SAL or MDMA; $n = 8$/group) are shown for the six pretreatment groups. Peripheral, central, and rearing activity are shown in the top, middle, and bottom panels respectively. The asterisks (*) denote activity levels that differed significantly from those of VEH-VEH-SAL rats. The carets (^) represent activity levels that differed significantly from those of VEH-VEH-MDMA rats. The number symbol (#) denotes activity levels that differed significantly from those of VEH-SB-MDMA rats ($p < .05$). Right panels: Data are presented as mean activity counts in each 5-min bin (± SEM) for the 90 min time period beginning immediately after the final injection (SAL or MDMA) for each of the pretreatment groups.

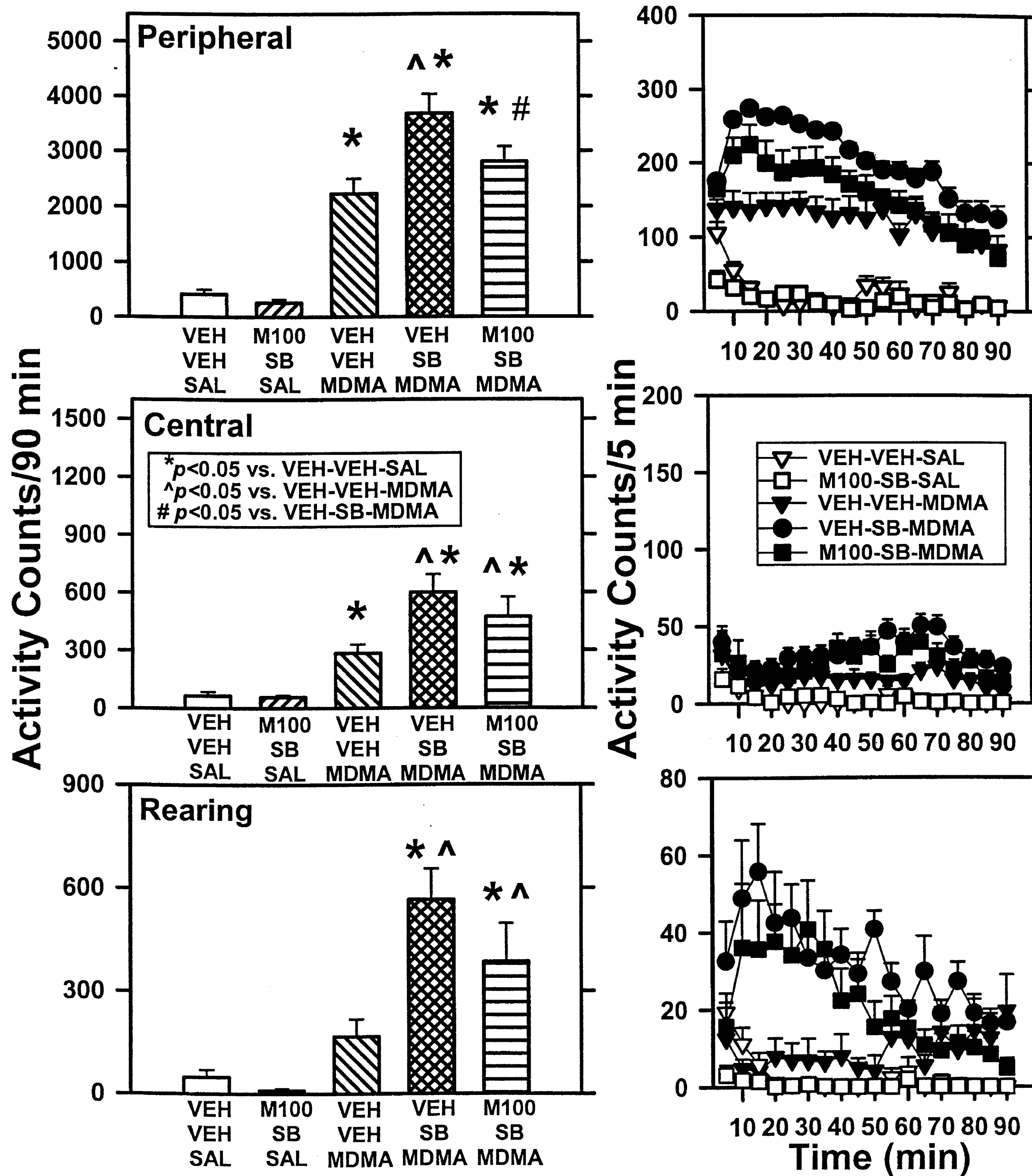

Figure 4. Effects of M100907 on SB 206553 plus (+)-MDMA hyperactivity. A group of rats (n = 8) was injected with M100907 (M100; 1.0 mg/kg i.p.) or β-cyclodextrin vehicle (VEH; 1 ml/kg i.p.) followed 15 min later by SB 206553 (SB; 2.0 mg/kg i.p.) or vehicle, and 30 min later with injection of (+)-MDMA (MDMA; 3 mg/kg s.c.) or saline (SAL; 1 ml/kg s.c.). Recording of activity began immediately in 5-min time periods and lasted for 90 min. Left panels: The mean activity counts (± SEM) summed over the 90 min period beginning immediately after the final injection (SAL or MDMA; n = 8/group) are shown for the pretreatment groups. Peripheral, central, and rearing activity are shown in the top, middle, and bottom panels respectively. The asterisks (*) denote activity levels that differed significantly from those of VEH-VEH-SAL rats. The carets (^) represent activity levels that differed significantly from those of VEH-VEH-MDMA rats. The number symbols (#) denote activity levels that differed significantly from those of VEH-SB-MDMA rats ($p < .05$). Right panels: Data are presented as mean activity counts in each 5-min bin (± SEM) for the 90 min time period beginning immediately after the final injection (SAL or MDMA) for each of the pretreatment groups.

min. A repeated measures design was utilized and the presentation of drugs was counterbalanced to control for confounds due to the order of drug treatment. Tests were spaced at least 48 h apart over the course of a 2–4 week period; each rat received either four or six tests total. In tests of psychostimulants, animals received either two or three injections of (+)-MDMA or four injections of amphetamine which were spaced at least four days apart over the course of testing.

To test the hypothesis that blockade of 5-$HT_{2B/2C}$R by SB 206553 would potentiate (+)-MDMA-evoked activity, four groups of rats (n = 8/group) were administered a dose of SB 206553 (either 0.5, 1.0, 2.0 or 4.0 mg/kg) or β-cyclodextrin vehicle (45% (w/v); 1 ml/kg, i.p.) followed by an injection of either (+)-MDMA (3 mg/kg, s.c.) or saline (0.9%; 1 ml/kg, s.c.) in a repeated measures design in which each rat received each of the four drug combinations spaced as indicated on the time line in Figure 1 (vehicle-saline, vehicle-(+)-MDMA, SB 206553-saline, SB 206553-(+)-MDMA). The ability of the 5-$HT_{1B/1D}$R antagonist GR 127935 (2.5 mg/kg; McCreary and Cunningham 1999; McCreary et al. 1999) or the 5-HT_{2A}R antagonist M100907 (1 mg/kg; McMahon and Cunningham 2001a,b) to block SB 206553 (2 mg/kg) plus (+)-MDMA (3 mg/kg) hyperactivity was also tested in separate groups of rats (n = 8/group). Lastly, to explore the ability of SB 206553 (2 mg/kg) to alter the activity profile of a DA or 5-HT releaser, studies were conducted in separate groups of rats (n = 8/group) with the DA releaser amphetamine (0.5 mg/kg) administered alone or in combination with the 5-HT releaser fenfluramine (4 mg/kg).

Drugs

Amphetamine (d-amphetamine), β-cyclodextrin (2-hydroxypropyl-β-cyclodextrin), fenfluramine ((±)-fenfluramine) and SB 206553 (N-3-pyridinyl-3,5-dihydro-5-methylbenzo(1,2-b:4,5-b′)dipyrrole-1(2H)carboxamide) were obtained from Research Biochemicals, Inc. (Natick, MA). GR 127935 ((2′-methyl-4′-(5-methyl-(1,2,4)oxadiazol-3-yl)biphenyl-4-carboxylic acid (4-methoxy)-3-(4-methylpiperazin-1-yl)phenyl)amide) was supplied by Glaxo-Wellcome (Ware, Hertfordshire, UK) and M100907 (R-(+)-α-(2,3-dimethoxyphenyl)-1-(2-(4-fluorophenylethyl))-4-piperidine-methanol) by Hoechst Marion Roussel (Cincinnati, OH). (+)-MDMA (3,4-methylenedioxymethamphetamine) was obtained from the National Institute on Drug Abuse (NIDA, Research Triangle Park, NC). Doses refer to the weight of the salt. Amphetamine, fenfluramine and (+)-MDMA were dissolved in 0.9% saline and administered subcutaneously (s.c.). SB 206553 was dissolved in 45% β-cyclodextrin in 0.9% saline with mild heating, while GR 127935 and M100907 were dissolved in 10% β-cyclodextrin in 0.9% saline with mild heating; all antagonists were administered intraperitoneally (i.p.). The vehicle matched with each drug consisted of the solution utilized for dissolution of a given drug. Verification that the compounds had dissolved was made visually.

Statistical Analyses

Total activity counts were summed for each individual rat across the 90-min observation period. Data are presented as mean total activity counts (± SEM) and the dependent measures were total peripheral, central and vertical activity observed during the 90 min test session. Because group comparisons were specifically defined prior to the start of the experiment, these planned comparisons were conducted in lieu of an overall F test in a multifactorial ANOVA; this statistical analysis has been supported in a number of statistical texts (e.g., Keppel 1973). Thus, each experiment was subjected to a one-way ANOVA for repeated measures with levels of the treatment factor corresponding to the drug combinations administered to that group. Planned, pairwise comparisons of the treatment means were made with least significant difference test (Keppel 1973; SAS for Windows, Version 6.12) which were conducted with an experimentwise error rate of $\alpha=0.05$.

To establish the dose-response curve for SB 206553 to potentiate (+)-MDMA-induced activity, it was necessary to normalize the activity levels for each of the rats from four different groups. To this end, the average number of peripheral, central or rearing activity counts observed during the 90-min session following injection with vehicle plus saline was established for all rats (n = 32) in the four pretreatment groups. This average value was subtracted from the total activity counts during the 90 min session following administration of (+)-MDMA (n = 32) or SB 206553 (0.5, 1, 2 or 4 mg/kg) plus (+)-MDMA (n = 8/group) to provide a change from baseline value. Variances were homogeneous and a parametric one-way ANOVA for independent measures followed by a Dunnett's test was used to compare the change from control activity levels at each dose of SB 206553 plus (+)-MDMA to that seen following vehicle plus (+)-MDMA.

RESULTS

The ability of SB 206553 to affect (+)-MDMA (3 mg/kg) evoked hyperactivity was assessed in four separate groups of animals using a repeated measures design and data were normalized as a change from the vehicle-saline baseline (Figure 2). A main effect of treatment was observed for measures of peripheral ($F_{4,59}=19.594$, $p = .0001$), central ($F_{4,59}=9.992$, $p=.0001$) and rearing activity ($F_{4,59}=16.2$, $p=.0001$). A priori analyses by Dunnett's test indicated a dose-related increase in (+)-MDMA-evoked

hyperactivity induced by SB 206553 with peripheral activity significantly enhanced by 1, 2 and 4 mg/kg of SB 206553; central and rearing activity were significantly enhanced by 1 and 2 mg/kg of SB 206553 (Figure 2).

An example of the effects of SB 206553 (2 mg/kg) on the activity profile induced by (+)-MDMA (3 mg/kg) is illustrated in Figure 3. A main effect of pretreatment was evident for peripheral ($F_{5,42}$=34.13, p = .0001), central ($F_{5,42}$=23.98, p = .0001) and rearing activity ($F_{5,42}$=14.12, p = .0001). A priori analyses revealed that (+)-MDMA (Figure 3) significantly increased peripheral, central and rearing activity compared with vehicle-saline rats ($p < .05$). Pretreatment with SB 206553 (2 mg/kg) prior to an injection of saline did not alter activity, although SB 206553 significantly enhanced peripheral, central and rearing activity induced by (+)-MDMA (Figure 3; $p < .05$). The timecourse of the effects on activity is shown in the right panels. A dose of GR 127935 (2.5 mg/kg), previously shown to completely block the hyperactivity evoked by 3 mg/kg of (+)-MDMA alone (McCreary et al. 1999), significantly attenuated the peripheral and rearing ($p < .05$), but not central, activity generated by SB 206553 plus (+)-MDMA. This notwithstanding, central and rearing activity levels observed following GR 127935 in combination with SB 206553 plus (+)-MDMA were significantly elevated over vehicle plus (+)-MDMA levels ($p < .05$).

A separate group of rats was utilized to assess the ability of M100907 (1 mg/kg) to alter the behavioral profile of SB 206553 plus (+)-MDMA. A main effect of pretreatment was evident for peripheral ($F_{4,35}$=39.83, p = .0001), central ($F_{4,35}$=13.7, p = .0001) and rearing activity ($F_{4,35}$=11.72, p = .0001). This dose of M100907 did not alter the hyperactivity induced by 3 mg/kg of (+)-MDMA (data not shown). In the present experiment, M100907 significantly attenuated peripheral activity induced by SB 206553 plus (+)-MDMA ($p < .05$), but had no effect on central and rearing activity; resulting levels of peripheral activity were still significantly higher than those seen after vehicle plus saline injection (Figure 4). On the other hand, in a group of rats (Figure 5) pretreated with both GR 127935 (2.5 mg/kg) and M100907 (1 mg/kg), a main effect of pretreatment was evident for peripheral ($F_{4,35}$=16.78, p = .0001), central ($F_{4,35}$=11.46, p = .0001) and rearing activity ($F_{4,35}$=6.29, p = .0001). Pretreatment with both GR 127935 and M100907 significantly reduced peripheral, central and rearing activity induced by SB 206553 plus (+)-MDMA ($p < .05$), although peripheral, central and rearing activity were still significantly higher than vehicle plus saline levels (Figure 5). Co-pretreatment with GR 127935, M100907 and SB 206553 did not affect activity levels ($p > .05$; Figure 5).

The ability of fenfluramine, at a dose (4 mg/kg) which did not alter activity profiles when administered alone (data not shown), to elicit an additive effect with amphetamine (1 mg/kg) was assessed in a separate group of rats (n = 8). A main effect of pretreatment was evident for peripheral ($F_{4,35}$=17.61, p = .0001), central ($F_{4,35}$=4.15, p = .0074) and rearing activity ($F_{4,35}$=11.72, p = .0001). A priori analyses revealed that amphetamine significantly increased peripheral and central activity over vehicle-saline levels, and SB 206553 significantly elevated peripheral, but not central or rearing, activity observed after amphetamine alone ($p < .05$; Figure 6). Co-treatment with amphetamine plus fenfluramine resulted in greater peripheral, but not central or rearing, activity compared with amphetamine alone ($p < .05$). SB 206553 further increased levels of peripheral, central and rearing activity observed following amphetamine plus fenfluramine ($p < .05$).

DISCUSSION

A low dose of (+)-MDMA increased locomotor activity, especially in the periphery of the activity monitor, without remarkable effects on rearing, a finding consistent with previous reports (Callaway et al. 1990; McCreary et al. 1999). The 5-$HT_{2B/2C}$R antagonist SB 206553 dose-dependently potentiated the hyperactivity caused by (+)-MDMA to a maximum 223% increase in peripheral activity, 318% increase in central activity, and 326% increase in rearing activity evoked by (+)-MDMA. These studies parallel the finding that the non-selective 5-$HT_{2/1}$R antagonist methysergide enhanced MDMA-induced hyperactivity (Gold and Koob 1988) and further suggest that antagonism of 5-HT_{2C}R accounts for this potentiative effect of SB 206553 (present results) and methysergide (Gold and Koob 1988) on MDMA-evoked hyperactivity. The highest dose of SB 206553 tested (4 mg/kg) was less efficacious than lower doses, suggesting that the compound may lose selectivity for 5-$HT_{2B/2C}$R at the high end of the dose-effect curve.

Like (+)-MDMA administered alone (McCreary et al. 1999), the hyperactivity induced by SB 206553 plus (+)-MDMA occurred primarily in the periphery of the chamber. It is noteworthy that SB 206553 potentiated (+)-MDMA (3 mg/kg)-induced activity to a level seen with much higher doses of MDMA (Kehne et al. 1996) or moderate doses of amphetamine (Callaway et al. 1990; Gold et al. 1989; Kelly et al. 1975) without altering the pattern of central and peripheral activity. However, in contrast to inconsistent (+)-MDMA-induced rearing seen here and previously (McCreary et al. 1999), there were reliable and robust increases in rearing after SB 206553 plus (+)-MDMA suggesting that activation of 5-HT_{2C}R consequent to (+)-MDMA administration may suppress rearing.

The protein for the 5-HT_{2C}R has been localized to both the nigrostriatal and mesoaccumbens DA pathways (Clemett et al. 2000) which have been implicated in the actions of psychostimulants. Transcript for the

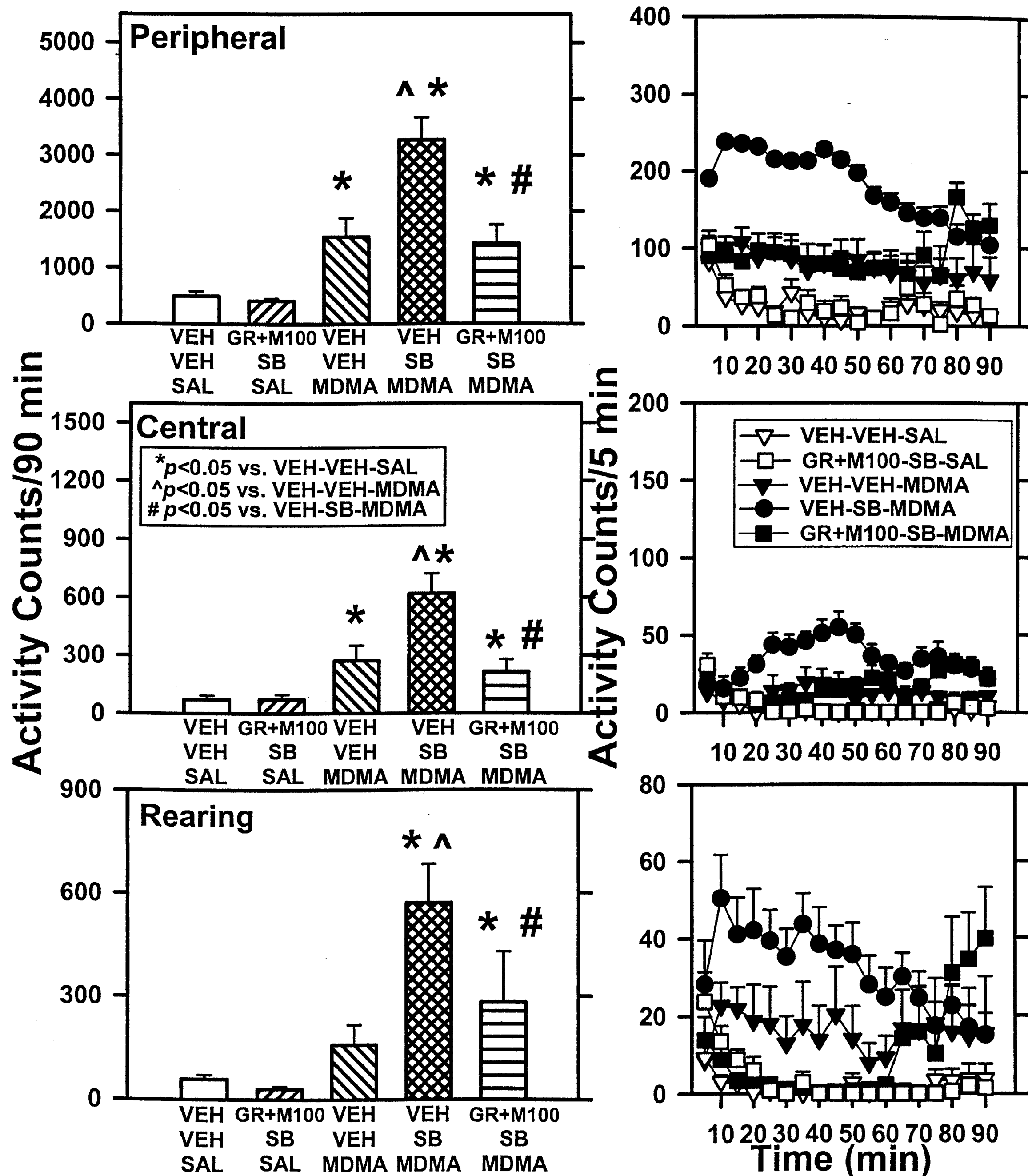

Figure 5. Effects of GR 127935 plus M100907 on SB 206553 plus (+)-MDMA hyperactivity. A group of rats ($n = 8$) was injected with GR 127935 (2.5 mg/kg) plus M100907 (M100; 1.0 mg/kg) or β-cyclodextrin vehicle (VEH; 1 ml/kg i.p.) followed 15 min later by SB 206553 (SB; 2.0 mg/kg i.p.) or vehicle, and 30 min later with injection of (+)-MDMA (MDMA; 3 mg/kg s.c.) or saline (SAL; 1 ml/kg s.c.) Recording of activity began immediately in 5-min time periods and lasted for 90 min. Left panels: The mean activity counts (± SEM) summed over the 90 min period beginning immediately after the final injection (SAL or MDMA; $n = 8$/group) are shown for the six pretreatment groups. Peripheral, central, and rearing activity are shown in the top, middle, and bottom panels respectively. The asterisks (*) indicate activity levels that differed significantly from those of VEH-VEH-SAL rats. The carets (^) denote activity levels that differed significantly from those of VEH-VEH-MDMA rats. The number symbol (#) indicates activity levels that differed significantly from those of VEH-SB-MDMA rats ($p < .05$). Right panels: Data are presented as mean activity counts in each 5-min bin (± SEM) for the 90 min time period beginning immediately after the second injection (SAL or MDMA) for each of the five pretreatment groups.

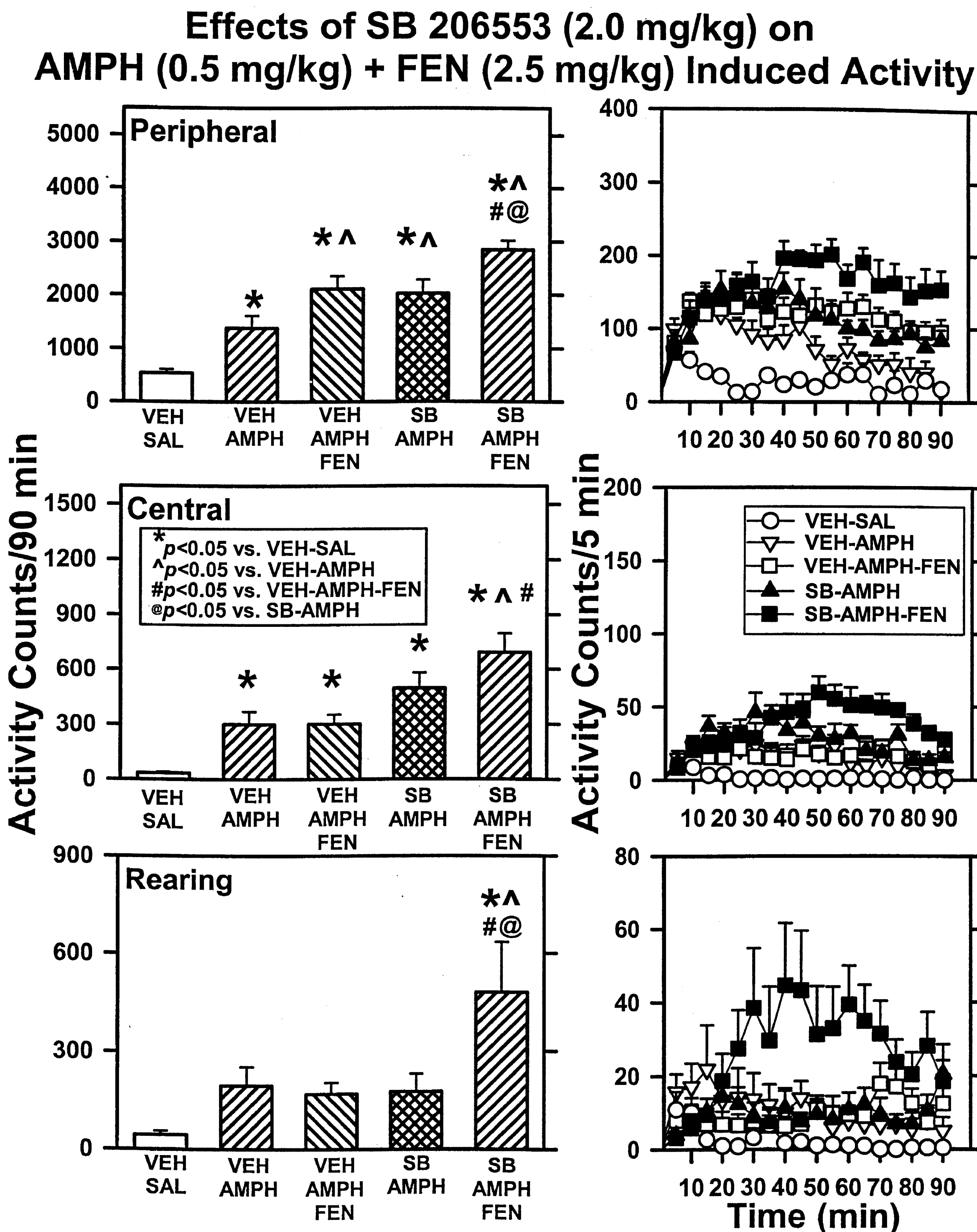

Figure 6. Effects of SB 206553 on amphetamine plus fenfluramine hyperactivity. A group of rats ($n = 8$) was injected with SB 206553 (SB; 2.0 mg/kg i.p.) or β-cyclodextrin vehicle (VEH; 1 ml/kg i.p.) followed 30 min later by injection of amphetamine (AMPH; 0.5 mg/kg) plus fenfluramine (FEN; 4 mg/kg s.c.) or saline (SAL; 1 ml/kg s.c.). Recording of activity began immediately in 5-min time periods and lasted for 90 min. Left panels: The mean activity counts (± SEM) summed over the 90 min period beginning immediately after SAL, AMPH, or AMPH-FEN ($n = 8$/group) are shown for the six pretreatment groups. Peripheral, central, and rearing activity are shown in the top, middle, and bottom panels respectively. The asterisks (*) denote activity levels that differed significantly from those of VEH-SAL rats. The carets (^) indicate activity levels that differed significantly from those of VEH-AMPH rats ($p < .05$). The number symbol (#) indicates activity levels that differed significantly from those of VEH-AMPH-FEN rats ($p < .05$). The at symbol (@) indicates activity levels significantly different from those of SB-AMPH rats ($p < .05$). Right panels: Data are presented as mean activity counts in each 5-min bin (± SEM) for the 90 min time period beginning immediately after the injection with SAL, AMPH or AMPH-FEN for each of the six pretreatment groups.

$5\text{-}HT_{2C}R$ has also been localized to regions containing DA cell bodies such as the substantia nigra (SN) and ventral tegmental area (VTA) as well as the terminals of DA pathways in the dorsal and ventral striatum (Eberle-Wang et al. 1997; Pompeiano et al. 1994). Expression of $5\text{-}HT_{2C}R$ mRNA colocalized with glutamic acid decarboxylase (GAD), but not tyrosine hydroxylase, in SN and VTA neurons suggests that the $5\text{-}HT_{2C}R$ is located in γ–aminobutyric acid (GABA), but not DA, neurons in the SN and VTA (Eberle-Wang et al. 1997). Thus, $5\text{-}HT_{2C}R$-mediated control of GABA input to DA neurons may provide one mechanism through which $5\text{-}HT_{2C}R$ could affect DA function. In fact, the finding that the indirect GABA agonist γ-vinyl GABA significantly lowered cocaine-induced elevations in striatal DA concentration and locomotor activity (Dewey et al. 1997), is in line with the possibility that the $5\text{-}HT_{2C}R$ influences DA neurotransmission, and thus the behavioral effects of this psychostimulant, via GABAergic mechanisms.

Although the specific brain sites at which the $5\text{-}HT_{2C}R$ exerts influence have not been determined, substantial evidence suggests that the $5\text{-}HT_{2C}R$ has an inhibitory role in the control of mesolimbic DA efflux. Systemic administration of $5\text{-}HT_{2C}R$ agonists depresses basal DA release in the NAc, slows the firing of VTA DA neurons (Di Matteo et al. 2000) and blocks cocaine-induced behavioral effects (Callahan and Cunningham 1995; Grottick et al. 2000). The $5\text{-}HT_{2B/2C}R$ antagonist SB 206553 potentiated DA efflux in the NAc (Di Matteo et al. 1998) and selective blockade of $5\text{-}HT_{2C}R$ by systemic administration of SB 242084 potentiated the firing of VTA DA neurons and elevated basal DA efflux in the NAc (Di Matteo et al. 1999). Systemic administration of SB 206553 also potentiated haloperidol-induced increases in striatal DA efflux, suggesting a role for $5\text{-}HT_{2C}R$ in the nigrostriatal DA pathway and the ability of these receptors to inhibit stimulated as well as basal DA efflux (Lucas et al. 2000). However, while $5\text{-}HT_{2C}R$ agonists suppress spontaneous behavior when administered alone (e.g., Grottick et al. 2000), prominent effects of $5\text{-}HT_{2C}R$ antagonists on spontaneous behavior have not been reported (present results; Grottick et al. 2000).

Due to the high affinity of SB 206553 for both $5\text{-}HT_{2B}R$ and $5\text{-}HT_{2C}R$, blockade of either or both receptors may account for the increase in locomotor activity seen when given in conjunction with (+)-MDMA. Modest levels of $5\text{-}HT_{2B}R$ are found in brain (Duxon et al. 1997); however, empirical evidence to support or refute a role for central or peripheral $5\text{-}HT_{2B}R$ in behavior is limited (see McCreary and Cunningham 1999, for discussion). Furthermore, the similarity of effects on DA efflux seen with SB 206553 and the selective $5\text{-}HT_{2C}R$ antagonist SB 242084 (which has little affinity for $5\text{-}HT_{2B}R$; Di Matteo et al. 1999) indicate that the behavioral outcome of pretreatment with SB 206553 is probably due to $5\text{-}HT_{2C}R$ antagonism.

A substantial body of literature suggests that $5\text{-}HT_{1B/1D}R$ activation following MDMA-induced 5-HT release is required for MDMA-induced increases in locomotion (Callaway et al. 1992; McCreary et al. 1999). However, the present results indicate that the activity evoked by the combination of SB 206553 plus (+)-MDMA is not completely dependent upon $5\text{-}HT_{1B/1D}R$ activation (unlike (+)-MDMA alone; McCreary et al. 1999). Blockade of $5\text{-}HT_{1B/1D}R$ with GR 127935 at a dose (2.5 mg/kg) that completely suppressed activity induced by 3 mg/kg of (+)-MDMA (McCreary et al. 1999) resulted in a modest, but non-significant, reduction in peripheral and central activity and a significant reduction in rearing compared with the levels obtained upon administration of SB 206553 plus (+)-MDMA. However, all measures of activity were still significantly higher than those produced by administration of (+)-MDMA alone. These results suggest that blockade of $5\text{-}HT_{2B/2C}R$ by SB 206553 does not merely potentiate a $5\text{-}HT_{1B/1D}R$-mediated hyperactivity, but unmasks hyperactivity mediated through other 5-HT receptors and/or neurotransmitter systems.

In an assessment of whether the $5\text{-}HT_{2A}R$ might underlie the potentiated hyperactivity induced by SB 206553 plus (+)-MDMA, we found that the $5\text{-}HT_{2A}R$ antagonist M100907 did modestly attenuate peripheral, but not central and rearing, activity evoked by the combination of drugs. This suggests that the blockade of $5\text{-}HT_{2C}R$ unmasks effects mediated, at least in part, by the $5\text{-}HT_{2A}R$. While (+)-MDMA alone elicits a hyperactivity that is abolished by GR 127935, the combination of SB 206553 plus (+)-MDMA yields a hyperactivity which is attenuated by a $5\text{-}HT_{1B}R$ plus a $5\text{-}HT_{2A}R$ antagonist, but is abolished by neither drug alone. However, the combination of the $5\text{-}HT_{1B}R$ plus a $5\text{-}HT_{2A}R$ antagonist did block peripheral, central, and rearing behavior elicited by SB 206553 plus (+)-MDMA, but only to a level similar to that elicited by (+)-MDMA alone. Thus, the hyperactivity elicited by SB 206553 plus (+)-MDMA could be characterized as dependent upon the combined effects of $5\text{-}HT_{1B/1D}R$ and $5\text{-}HT_{2A}R$ activation and at least one other unknown hyperactivity-mediating factor that is unmasked by the antagonism of $5\text{-}HT_{2C}R$.

In order to ascertain the contributions of DA and 5-HT release to the observed effects of (+)-MDMA, we compared the ability of SB 205663 to alter the activity profile of the DA releaser amphetamine (Hernandez et al. 1987) and 5-HT releaser fenfluramine, respectively (Trulson and Jacobs 1976; Viana et al. 1996). Amphetamine (0.5 mg/kg) evoked a comparable level of hyperactivity to that seen with 3 mg/kg of (+)-MDMA, and pretreatment with SB 206553 potentiated amphetamine-evoked peripheral activity. This suggests that blockade of $5\text{-}HT_{2C}R$, even at presumably lower (vs. (+)-MDMA) levels of $5\text{-}HT_{2C}R$ activation, can potentiate the predominantly DAergic hyperactivity mediated by amphet-

amine. In contrast to amphetamine and as predicted from previous reports (Aulakh et al. 1988; Callaway et al. 1993), fenfluramine (4 mg/kg) did not significantly affect spontaneous activity nor did SB 206553 plus fenfluramine induce hyperactivity (data not shown). However, the combination of amphetamine plus fenfluramine did result in enhanced peripheral activity, as compared with amphetamine alone (present results). SB 206553 pretreatment further potentiated hypermotility evoked by amphetamine plus fenfluramine, particularly in measures of rearing activity. These data suggest that activation of 5-HT_{2C}R exerts an inhibitory influence on both amphetamine-evoked activity and the activity elicited by the combination of elevated DA and 5-HT produced by amphetamine plus fenfluramine. The finding that a combination of SB 206553 plus fenfluramine did not result in the elicitation of hyperactivity suggests that the blockade of 5-HT_{2C}R is incapable of unmasking locomotor activation mediated by 5-HT release secondary to fenfluramine, but is capable of further potentiation of the activity evoked by amphetamine plus fenfluramine.

The failure of the 5-$HT_{2B/2C}$R antagonist to unmask a "solely 5-HT–mediated" hyperactivity when combined with fenfluramine is interesting. Some of the behavioral effects of fenfluramine have been attributed to stimulation of the 5-HT_{2C}R (Kennett and Curzon 1988), and the 5-HT_{2C}R agonist MCPP, which has a moderate affinity for the 5-$HT_{1B/1D}$R (Kennett and Curzon 1988), exhibits a 5-$HT_{1B/1D}$R-dependent hyperactivity when administered in combination with a 5-HT_2R antagonist (Gleason and Shannon 1998) or in mutant mice lacking the 5-HT_{2C}R (Heisler and Tecott 2000). This suggests that 5-HT_{2C}R stimulation can mask 5-$HT_{1B/1D}$R-mediated hyperactivity. In the case of drugs that have a higher affinity for 5-HT_{2C}R than 5-$HT_{1B/1D}$R (as for MCPP; Barnes and Sharp 1999), the hyperactivity induced by the 5-HT_{1B}R can be counteracted by actions at the 5-HT_{2C}R. This explanation does not, however, resolve why indirect activation of 5-$HT_{1B/1D}$R following fenfluramine administration, even in the presence of SB 206553, did not result in hyperactivity. It appears that 5-HT–mediated hyperactivity may manifest only under very specific neurochemical circumstances.

In summary, the 5-HT_{2C}R has a large inhibitory influence upon the hyperactivity induced by a low dose of (+)-MDMA (3 mg/kg). Previous work from this laboratory has determined that blockade of 5-$HT_{1B/1D}$R abolishes the hyperactive response to a low dose of (+)-MDMA (McCreary et al. 1999), and superficially it seems that 5-$HT_{1B/1D}$R and 5-HT_{2C}R simply oppose each other. However, upon blockade of 5-HT_{2C}R with SB 206553, the hyperactivity that emerges upon (+)-MDMA administration is only partially dependent on both 5-$HT_{1B/1D}$R *and* 5-HT_{2A}R. The inability of SB 206553 to produce hyperactivity when combined with the 5-HT releaser fenfluramine along with the SB 206553-induced potentiation of amphetamine in the presence or absence of fenfluramine suggests that blockade of the 5-HT_{2C}R results in an unmasking of dopaminergically-mediated hyperactivity.

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