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ORIGINAL INVESTIGATION

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Role of 5-HT_{2A} and 5-$HT_{2C/B}$ receptors in the acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on striatal single-unit activity and locomotion in freely moving rats

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Abstract *Rationale:* Like amphetamine, a locomotor-activating dose of 3,4-methylenedioxymethamphetamine (MDMA) predominantly excites striatal single-unit activity in freely moving rats. Although both D_1- and D_2-like dopamine (DA) receptors play important roles in this effect, MDMA, unlike amphetamine, strongly increases both DA and serotonin (5-HT) transmission. *Objectives:* This study was conducted to investigate the 5-HT receptor mechanisms underlying the striatal effects of MDMA. *Methods:* We recorded the activity of >200 single units in the striatum of awake, unrestrained rats in response to acute MDMA administration (5 mg/kg) combined with the selective blockade of either 5-HT_{2A} or 5-$HT_{2C/B}$ receptors. *Results:* Prior administration of SR-46349B (a 5-HT_{2A} antagonist 0.5 mg/kg) blocked nearly all MDMA-induced striatal excitations, which paralleled its significant attenuation of MDMA-induced locomotor activation. Conversely, prior administration of SB-206553 (a 5-$HT_{2C/B}$ antagonist 2.0 mg/kg) had no effect on the amount of MDMA-induced locomotor activation or the distribution of single-unit responses to MDMA. However, a coefficient-of-variation analysis indicated significantly less variability in the magnitude of both MDMA-induced neuronal excitations and inhibitions in rats that were pretreated with SB-206553 compared to vehicle. Analysis of concurrent single-unit activity and behavior confirmed that MDMA-induced striatal activation was not merely due to behavioral feedback, indicating a primary action of MDMA. *Conclusion:* These results support and extend our previous findings by showing that 5-HT_{2A} and 5-$HT_{2C/B}$ receptors differentially regulate the expression of MDMA-induced behavioral and striatal neuronal responses, either directly or through the modulation of DA transmission.

Keywords 5-HT_{2A} · 5-$HT_{2C/B}$ · Drug abuse · Freely moving rat · MDMA · SB-206553 · Serotonin · Single-unit electrophysiology · SR-46349B · Striatum

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA; "ecstasy") is a ring-substituted amphetamine (AMPH), increasingly used by young adults at dance parties called "raves." Although there is some controversy regarding the safety of MDMA, it seems clear that MDMA is toxic to serotonin (5-HT) neurons in animals and possibly humans (Parrott 2002; Ricaurte et al. 2000). In fact, several MDMA-related emergency room visits and deaths have been reported (Dowling et al. 1987; Henry et al. 1992). MDMA's reinforcing effects are indicated by studies showing that MDMA exposure induces conditioned place preference (Marona-Lewicka et al. 1996; Meyer et al. 2002), facilitates the acquisition of cocaine self-administration (Fletcher et al. 2001), enhances intracranial self-stimulation (Reid et al. 1996), and serves as a reinforcer in a rat runway procedure (Wakonigg et al. 2003). Also of concern is MDMA's abuse potential, as evidenced by its ability to support self-administration in nonhuman primates (Beardsley et al. 1986; Fantegrossi et al. 2002; Lamb and Griffiths 1987) and rats (Cornish et al. 2003; Ratzenboeck et al. 2001; Schenk et al. 2003), as well as cause withdrawal symptoms in a large proportion of human users (Cottler et al. 2001).

MDMA increases release of monoamines, including dopamine (DA) (Matthews et al. 1989; Yamamoto and Spanos 1988), primarily by acting as a substrate for monoamine reuptake transporters (Crespi et al. 1997; Nash and Brodkin 1991). It is widely believed that increased DA transmission in striatum underlies the locomotor stimulant effects of AMPH-like stimulants (Fischman and Johanson 1996; Segal and Kuczenski 1994; Seiden et al. 1993). Studies in

freely moving animals have revealed that striatal neurons respond with both increases and decreases in firing rate after acute AMPH administration, but excitations constitute the greatest proportion of responses (Haracz et al. 1989, 1993; Rebec et al. 1991; West et al. 1997). Supporting a role for DA in this response, both nonselective DA antagonists and relatively selective D_1 and D_2 antagonists reverse AMPH-induced striatal excitations (Haracz et al. 1993; Rebec et al. 1991; Rosa-Kenig et al. 1993; Wang and Rebec 1993). Paralleling these results, we recently showed that a locomotor-activating dose of MDMA (5 mg/kg) had a predominantly excitatory effect on striatal neuronal activity in freely moving rats and that both the behavioral and electrophysiological effects were reversed by D_1 and D_2 receptor antagonists (Ball et al. 2003). Thus, it appears that the electrophysiological and pharmacological mechanisms underlying the acute behavioral effects of MDMA are not unlike those of its parent drug, AMPH.

However, unlike AMPH, a relatively selective releaser of catecholamines at locomotor-activating doses, MDMA also increases 5-HT transmission (Gough et al. 1991; Kankaanpaa et al. 1998), due to its affinity for the 5-HT transporter (Battaglia et al. 1988; Rudnick and Wall 1992). To further understanding of the 5-HT receptor mechanisms underlying the striatal response to MDMA, we recorded single-unit activity in the striatum of awake, unrestrained rats in response to acute MDMA administration (5 mg/kg) combined with the selective blockade of 5-HT_{2A} or 5-$HT_{2C/B}$ receptors, which are known to have differential effects on MDMA-induced locomotor activation (Bankson and Cunningham 2002; Fletcher et al. 2002; Kehne et al. 1996). DA efflux is also differentially modulated by these receptors in that 5-HT_{2A} and 5-$HT_{2C/B}$ receptors have a facilitatory and an inhibitory influence on DA efflux, respectively (Gobert et al. 2000; Lucas and Spampinato 2000; Schmidt et al. 1992). Thus, it was hypothesized that prior administration of either SR-46349B (SR) or SB-206553 (SB), 5-HT_{2A} and 5-$HT_{2C/B}$ antagonists, respectively, would have differential effects on both MDMA-induced locomotor activation and striatal single-unit activity.

Materials and methods

Animals

Data were obtained from male, Sprague–Dawley rats weighing 350–450 g and bred from source animals supplied by Harlan Industries (Indianapolis, IN). Animals were housed individually under standard laboratory conditions (12-h light cycle from 7:30 AM to 7:30 PM) with ad libitum access to food and water. All procedures were performed in compliance with the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2003), and approved by the Indiana University Institutional Animal Care and Use Committee.

Surgery and electrophysiology

Following subcutaneous (s.c.) injection of atropine sulfate (0.05 mg/kg) to minimize congestion, animals were anesthetized with intramuscular injections of ketamine HCl (90 mg/kg) and xylazine HCl (10 mg/kg) and then placed in a stereotaxic frame. After the skull was exposed, two small holes were drilled over dorsal striatum (1.00 mm anterior and 2.50 mm lateral to bregma), and the underlying dura was carefully retracted. Five additional holes were drilled for stainless steel support screws. Two electrode bundles were implanted bilaterally into dorsal striatum (depth 5.00 mm), then cemented to the skull and the support screws with dental acrylic. Each electrode bundle consisted of seven microwires (Formvar-coated stainless steel, 25-μm diameter, California Fine Wire Co., Grover Beach, CA) and one ground wire (stainless steel 50-μm diameter), soldered to an eight-pin connector (Omnetics Connector Corp., Minneapolis, MN).

For all experimental sessions, a flexible, shielded, wire harness was plugged into the connector on the rat's head. The rat was then placed into a sound-attenuating, open-field recording chamber (1.2 m^2), and the harness was connected to a ceiling-mounted electrical commutator, allowing the rat unrestricted movement. A white light bulb located at the top of one wall illuminated the chamber, and a video camera mounted above the rat recorded all experiments for subsequent behavioral analysis. Neuronal signals were amplified, filtered (band-pass 0.3–10 kHz) and passed through an analog-to-digital converter to a computer-based multiple neuron acquisition processor (MNAP, Plexon, Inc., Dallas, TX). To be classified as single-neuron activity, waveforms had to display a signal-to-noise ratio of at least 2.5:1 and exhibit consistent shape and amplitude. Analysis of autocorrelations also was used to support single-unit activity classification (Harris et al. 2000; Kosobud et al. 1994; Rieke et al. 1997). Specifically, units that displayed a trough in the autocorrelation at $t<10$ ms were considered to be single-neuron recordings. For each unit, data from the entire 120-min recording session (which includes pre- and post-MDMA activity) was used for autocorrelation analysis. This ensured that any extraneous noise due to increased movement was not counted as spike activity. In some cases, spikes with similar features (e.g., waveform, amplitude) were separated from other spikes and noise events by cluster analysis. Clustered spikes were well separated from other spikes recorded simultaneously to ensure single-unit isolation (Schmitzer-Torbert et al. 2005). Any recordings not meeting the above criteria were excluded from subsequent analyses.

Experimental sessions

After 4–6 days of recovery from surgery, animals were habituated to the recording chamber for 3 h. All experiments were conducted between 9:00 AM and 5:00 PM.

Before the commencement of each experimental session, rats were placed into the recording chamber and unit activity was discriminated. Because many medium spiny striatal neurons are silent during quiet rest, some units fired little, if at all, when the rat was still. If a rat did not exhibit sufficient spontaneous activity to adequately discriminate these types of units, the animal was prompted to move either by turning off the house light or moving it to the opposite corner of the recording chamber. In some cases, units could be induced to fire by waving a hand or snapping the fingers near the animal. After all units were discriminated (~20 min), experimental recording sessions began. Sessions were 120 min in length and divided into three successive periods, as illustrated in Fig. 1. Period 1 (20 min) served as baseline, during which no treatment was administered. Period 2 (15 min) began 5 min after the administration of one of three treatments: vehicle (VEH 1.0 ml/kg of either saline or β-cyclodextrin, s.c.; n=7 rats), SR (0.5 mg/kg, s.c.; n=5 rats), or SB (2.0 mg/kg, s.c.; n=5 rats). Period 3 (75 min) began 5 min after an injection of MDMA (5.0 mg/kg, s.c.) for all animals.

Drugs

(±)-MDMA was provided by the National Institute on Drug Abuse (NIDA, Research Triangle Park, NC). SR-46349B (*trans*-4-[(3*Z*)3-[(2-dimethylaminoethyl)oxiimino]-3-(2-fluorophenyl)propen-1-yl]-phenol, hemifumarate) was provided by Sanofi Synthelabo Recherche (Montpellier, France). SB-206553 (5-methyl-1-(3-pyridylcarbamoyl)-1,2,3,5-tetrahydropyrrolo[2,3-*f*]indole hydrochloride) was obtained from Sigma Biochemicals (St. Louis, MO). All doses refer to the weight of the salt. MDMA and SB-206553 were dissolved in 0.9% saline. SR-46349B was dissolved in 2-hydroxypropyl-β-cyclodextrin (45% [w/v] solution in water). The dose of MDMA chosen for this study is a dose that we have used previously because it causes negligible neurotoxicity in rats (Fone et al. 2002; Kalivas et al. 1998; O'Shea et al. 1998; Slikker et al. 1989), yet induces a robust increase in locomotor activation (Ball et al. 2003; Spanos and Yamamoto 1989). The doses of SR-46349B and SB-206553 were chosen to ensure maximal blockade of either 5-HT_{2A} or 5-$HT_{2C/B}$ receptors, with minimal interaction at other binding sites (Kennett et al. 1996; Schreiber et al. 1995).

Histology

After completion of experiments, rats were deeply anesthetized with chloropent (3.3 ml/kg, i.p.), and marking lesions were made by applying a 7-s, 40-μA current across those wires from which units were recorded. Rats were then perfused transcardially with saline, followed by a solution of 4% paraformaldehyde and 5% potassium ferrocyanide. After storage in formaldehyde solution, brains were frozen, cut (60 μm sections), mounted on slides, and stained with cresyl violet to verify recording sites.

Data analysis

A mean baseline firing rate was obtained for each unit during the last 5 min of period 2. Changes in firing rate for individual units were calculated as a percentage of baseline for each 5-min bin in period 3. During quiet-resting behavior, the majority of striatal units exhibit fairly regular low levels of spontaneous activity (Ball et al. 2003; Haracz et al. 1993, 1998). However, during phasic behavioral activation (e.g., locomotion), it is not uncommon to observe changes in firing rate of >100% (Haracz et al. 1993; Rosa-Kenig et al. 1993). Therefore, increases or decreases in firing rate of >50% for at least three consecutive bins were classified as excitations or inhibitions, respectively (Ball et al. 2003; Haracz et al. 1993). Differences in the frequency of excitations and inhibitions between groups were evaluated with a Pearson Chi-square test. A coefficient-of-variation analysis was also applied to the electrophysiological data to determine the amount of variability in the magnitude of excitation or inhibition between individual neurons in a treatment group. Excited and inhibited units were analyzed separately by dividing the standard deviation of the magnitude of excitation or inhibition by the mean magnitude of excitation or inhibition for each 5-min bin after MDMA administration. Coefficients of variation between VEH/MDMA and SB/MDMA groups were then compared with *t*-tests.

A trained observer, blind to the treatment conditions, viewed videotapes of experimental sessions and scored locomotion using event-recording software (BEST Collection, Educational Consulting Inc., Las Vegas, NV) as reported previously (Ball et al. 2003). To define baseline locomotion, three 1-min samples were collected during period 2 in ranges 25–26, 30–31, 35–36, and 39–40 min into the

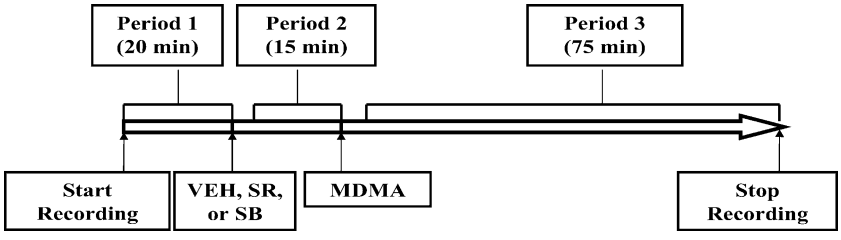

Fig. 1 Timeline of recording protocol. The time between each treatment (VEH, SB, or SR) was 20 min; the period for data analysis began 5 min after injection to avoid confounds due to the injection procedure. All animals were used only once to avoid confounds associated with sensitization to repeated MDMA administrations (Kalivas et al. 1998; Spanos and Yamamoto 1989)

session and averaged for each animal. Period 3 was partitioned into 5-min segments and data were collected during the first min of each 5-min bin beginning 5 min after MDMA injection. Locomotion for each animal was calculated as a percentage of baseline for each 1-min bin in period 3. A mean locomotor baseline was calculated for all animals in a group; this baseline was then used to calculate the percentage of baseline locomotion for individual animals in that group. For each group, a one-way, repeated-measures analysis of variance (ANOVA) was applied to the locomotion data, with 1-min bins as the within-subjects factor. For comparison of locomotion between groups, the post-MDMA period was divided into three ~30-min blocks, and planned comparisons were conducted for each block using a one-way ANOVA with treatment as the between-subjects factor. This 30-min interval was used in our previous study (Ball et al. 2003), and was based on work by Kehne et al. (1996). Pairwise comparisons for each block were made with Fisher's least significant difference test.

An additional analysis was applied to data from the VEH/MDMA group. We analyzed units classified as excited when pre- and post-MDMA behavior was held constant or "clamped" (Haracz et al. 1993, 1998). For this analysis, we compared the firing rate of individual units during discrete instances of comparable locomotion before and after MDMA administration. Comparisons between firing rates during quiet rest, pre- and post-MDMA locomotion were compared with a repeated-measures ANOVA followed by Fisher's least significant difference test for pairwise comparisons.

Results

Predrug behavior and single-unit activity

We recorded a total of 222 striatal units from 14 rats (see Fig. 2 for electrode bundle placements). Pre-MDMA behavior (period 2) consisted of quiet rest with occasional bouts of locomotion or grooming. During this period, all neurons had a mean (±SEM) firing rate of 2.75 (±0.23) spikes/s. The vast majority of neurons had slow (<7 spikes/s), irregular rates of activity; however, the range of firing rates was from 0.01 to 28.28 spikes/s, and the median firing rate was 1.64 spikes/s. Action potential waveforms were short duration (<2 ms) and biphasic, consistent with previous

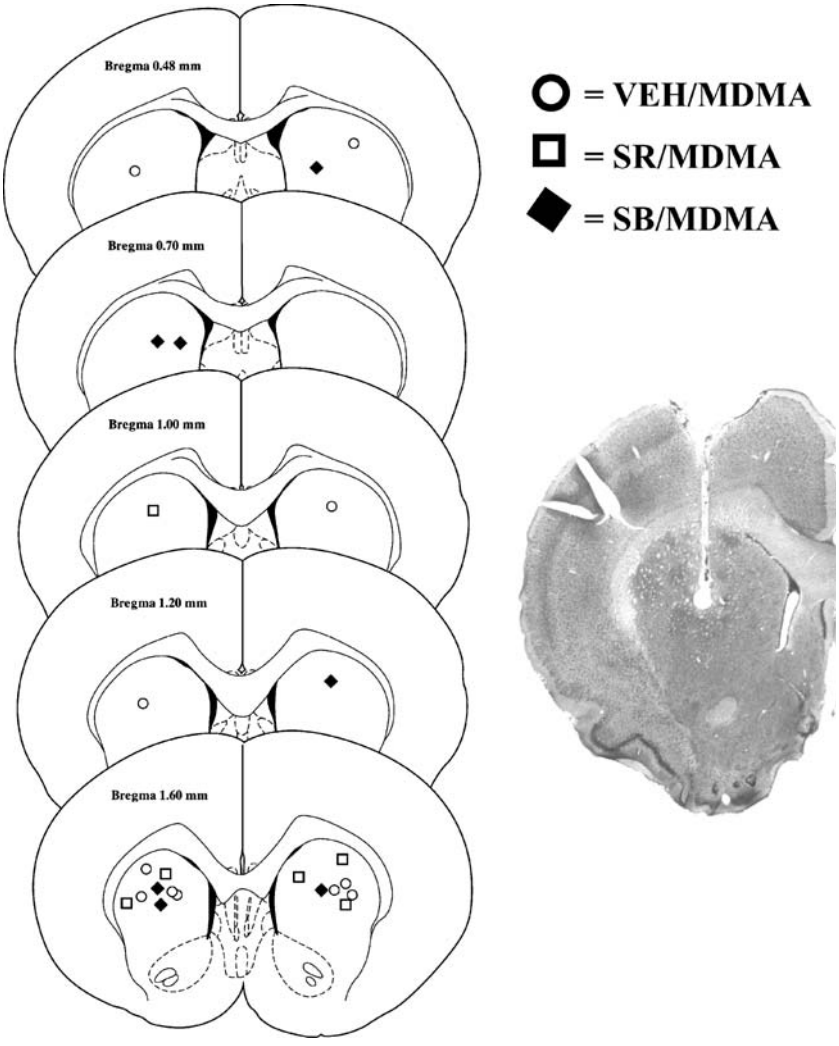

Fig. 2 Schematic illustration of coronal sections of rat brain showing approximate location of electrode bundle tips in dorsal striatum (modified from Paxinos and Watson 1998). See figure legend for placements of respective groups. *Inset*: Photomicrograph of coronal section illustrating electrode bundle tract and lesion. Notch indicates right hemisphere

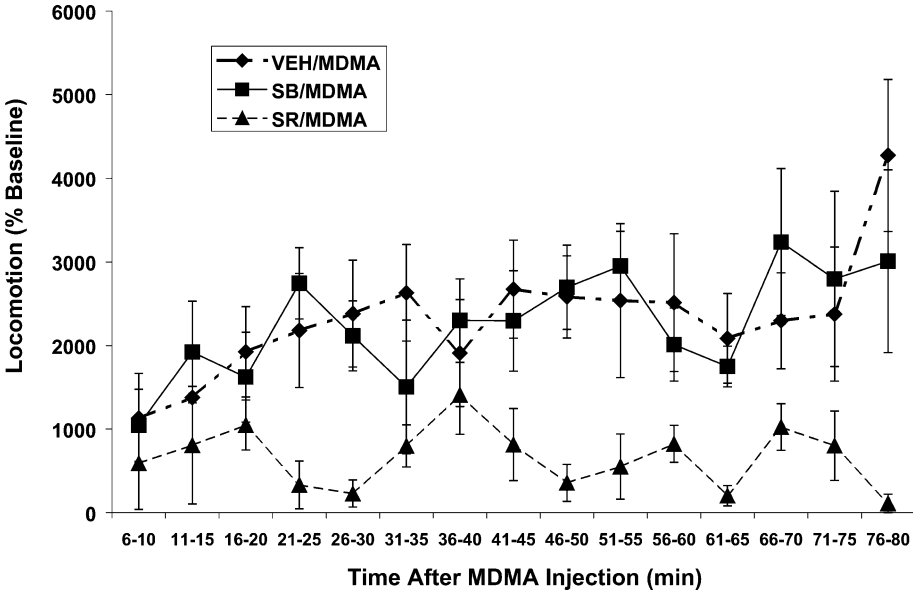

Fig. 3 Effect of VEH, SB (2.0 mg/kg), and SR (0.5 mg/kg) on MDMA-induced locomotor activation. Vehicle and 5-HT antagonists were given 20 min prior to MDMA (5.0 mg/kg) administration. Curves represent mean (±SEM) locomotion calculated as a percentage of baseline (i.e., quiet-resting behavior with occasional bouts of locomotion or grooming) for each 5-min bin beginning 5 min post-MDMA injection

striatal recordings in freely moving rats (Ball et al. 2003; Haracz et al. 1993, 1998). There were no significant differences in basal (i.e., period 2) electrophysiological characteristics or amount of locomotion between groups of animals receiving VEH, SB, or SR. Also, we found no significant differences in basal firing rates between units that displayed different responses to MDMA (i.e., excitation, inhibition, or no response).

Drug effects on behavior

A significant increase in locomotion in response to MDMA [$F(16,96)=4.93$, $p<0.001$] occurred within 10 min of injection and persisted throughout the remainder of the experiment (see Fig. 3). Similar to other reports (Ball et al. 2003; Gold et al. 1988; McCreary et al. 1999), this locomotion occurred predominantly along the perimeter of the recording chamber. The mean (±SEM) increase in locomotion peaked at 4,272 (±910) % of baseline during the last bin of behavioral recording (79–80 min post-MDMA).

Prior administration of either SB or SR had differential effects on MDMA-induced behaviors. MDMA administration in the SB/MDMA group significantly increased locomotion [$F(16,64)=3.12$, $p<0.001$] to levels comparable to VEH/MDMA (see Fig. 3). Mean (±SEM) locomotion peaked at 3,235 (±880) % of baseline 70–71 min post-MDMA. Conversely, MDMA-induced locomotion in the SR/MDMA group was largely attenuated (see Fig. 3). Locomotor activity peaked at a mean (±SEM) of 1,408 (±471) % of baseline, but this was not a statistically significant increase compared to baseline. Further analysis showed that when the post-MDMA period was divided into early, middle, and late periods, SR significantly blocked MDMA-

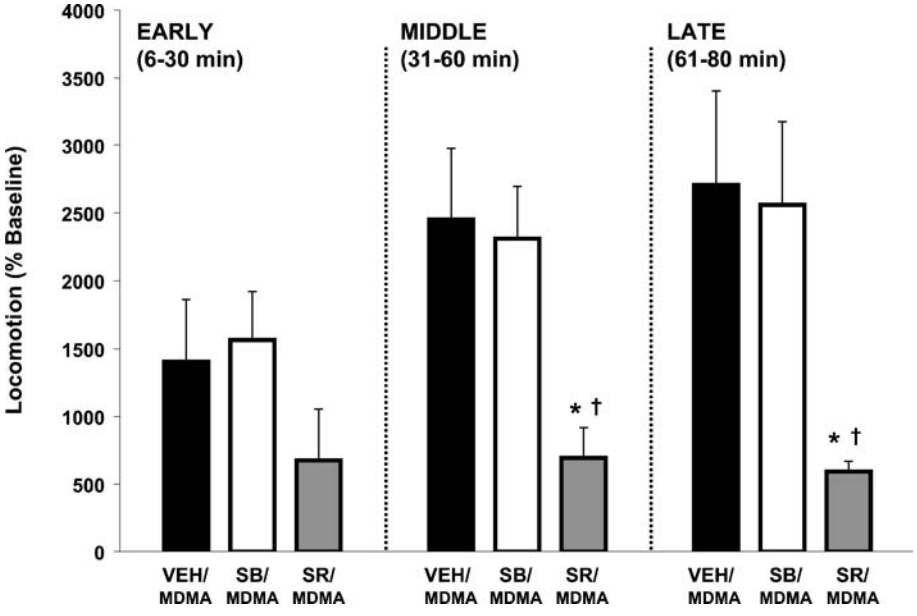

Fig. 4 Comparison of the effects of prior administration of VEH, SB, and SR on MDMA-induced locomotor activation during three phases of the MDMA response. Error bars represent SEM. *Asterisk* above SR/MDMA group denotes a significant difference from VEH/MDMA group, $p<0.05$. *Dagger* above the SR/MDMA group signifies a significant difference from the SB/MDMA group, $p<0.05$

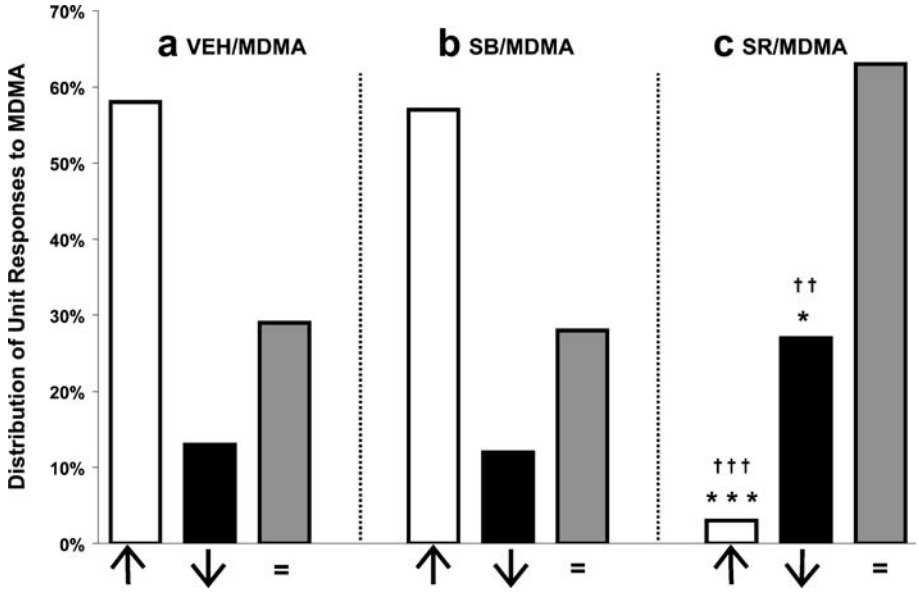

Fig. 5 Proportion of units per group excited (↑), inhibited (↓), and nonresponsive (=) after MDMA treatment. Units showing increases or decreases in activity by >50% of baseline for at least three consecutive bins were classified as excited or inhibited, respectively. If these criteria were not met, a unit was classified as unresponsive. *Asterisk* denotes a significant difference in frequency compared to the same response category in the VEH/MDMA group: *$p<0.05$; ***$p<0.001$. *Dagger* indicates a significant difference in frequency compared to the same response category in SB/MDMA group: $^{\dagger\dagger}p<0.01$; $^{\dagger\dagger\dagger}p<0.001$

induced locomotion compared to both VEH and SB during the middle [$F(2,14)=4.60$, $p<0.05$] and late [$F(2,14)=3.75$, $p<0.05$] periods (see Fig. 4).

Drug effects on striatal neurons

MDMA administration had a predominantly excitatory effect on neuronal activity. Forty-five out of 77 units in the VEH/MDMA group increased activity in response to MDMA compared to baseline (see Fig. 5a). The mean (±SEM) neuronal excitation peaked at 2,045 (±1072) % of baseline during the 5-min bin occurring between 65 and 70 min post-MDMA injection. The vast majority of these units (37/45) became excited within 10 min after MDMA administration. A small proportion of units (10/77) was inhibited by MDMA, and all but one of these units displayed reductions in firing rate within the first 10 min of drug treatment. Mean (±SEM) inhibition reached 20 (±7) % of baseline between 60 and 65 min post-MDMA.

The distribution of unit responses in the SB/MDMA group was nearly identical to the VEH/MDMA group (see Fig. 5b). Most units (49/86) displayed excitations within the first 10 min after MDMA administration. Mean (±SEM) excitation peaked at 567 (±137) % of baseline during the last 5-min bin of recording. Ten out of 86 neurons were inhibited by MDMA, and these inhibitions also had a short latency. Mean (±SEM) inhibition reached 33 (±7) % of baseline between 10 and 15 min post-MDMA. Three units displayed a multiphasic response, which was manifest as an

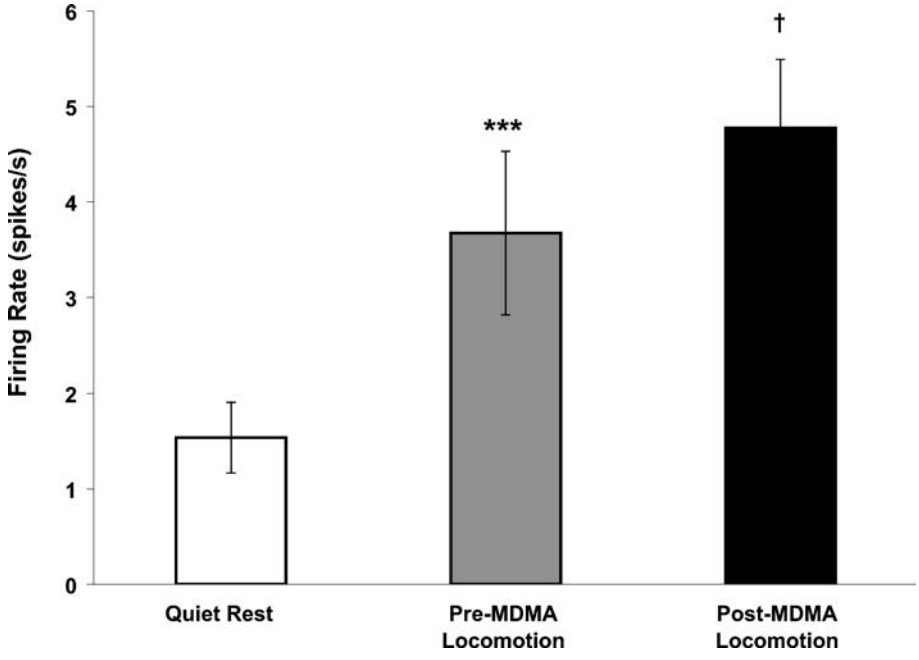

Fig. 6 Results of behavioral clamping analysis. Bars indicate mean (±SEM) firing rates for all units in VEH/MDMA group that were categorized as excited by MDMA relative to pre-MDMA firing rates. Quiet rest refers to mean firing rates during the last 5 min of period 2 (quiet-resting behavior with occasional bouts of locomotion or grooming). Pre- and post-MDMA locomotion refer to firing rates during discrete instances of locomotion before and after MDMA administration, respectively. At the 5 mg/kg dose, MDMA-induced locomotor activity closely resembled normal exploratory locomotion displayed before drug injection. *Asterisks* denote a significant difference from quiet rest condition, $p<0.001$. *Dagger* indicates a significant difference from pre-MDMA locomotion condition, $p<0.05$

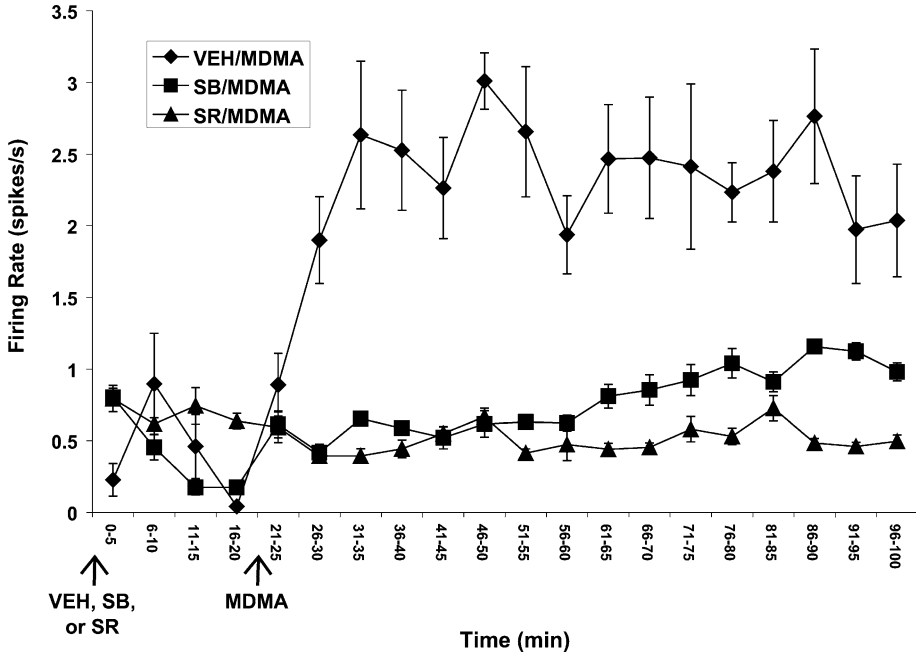

Fig. 7 Examples of activity from representative neurons with similar baseline firing rates in each treatment group. Data are plotted as mean (±SEM) spikes/s in 5-min bins. Points without error bars indicate the SEM is too small to illustrate. *Arrows* indicate respective injection times. Note that the predominant effect of SR/MDMA was no change from baseline. Although the predominant response in both the VEH/MDMA and SB/MDMA groups was excitation, the typical neuron in the VEH/MDMA group displayed a greater magnitude of excitation compared to the SB/MDMA group

early excitation followed in turn by an inhibition and a subsequent excitation.

As Fig. 5c illustrates, prior administration of SR blocked all but two MDMA-induced striatal excitations, which paralleled its attenuation of MDMA-induced locomotor activation. This difference in frequency of excitations was significant: χ^2 (1, N=136)=44.76, p<0.001 and χ^2 (1, N=145)=44.07, p<0.001 for SR/MDMA vs VEH/MDMA and SR/MDMA vs SB/MDMA, respectively. Thus, the majority of neurons in the SR/MDMA group (37/59) was nonresponsive to MDMA treatment. A smaller proportion of neurons (16/59) showed inhibitions following MDMA, but this effect occurred significantly more frequently than in either the VEH/MDMA or SB/MDMA groups: χ^2 (1, N=136)=4.31, p<0.05 and χ^2 (1, N=145)=5.70, p<0.01 for SR/MDMA vs VEH/MDMA and SR/MDMA vs SB/MDMA, respectively. Mean (±SEM) inhibition reached 38 (±10) % of baseline. Four remaining units were classified as multiphasic. Two of these units were inhibited early and excited late in the post-MDMA period, while the remaining two responded in the reverse manner.

To rule out behavioral feedback as the sole reason for changes in neuronal activity, we compared the firing rates of all neurons categorized as excited in the VEH/MDMA group during similar instances of locomotion both before and after MDMA administration. As Fig. 6 shows, this analysis revealed that firing rates during pre-MDMA bouts of locomotion were significantly higher compared to quiet-resting behavior, and firing rates during post-MDMA bouts of locomotion increased even further [F(2,88)=22.29, p<0.001].

The magnitude of excitation of the typical neuron in the VEH/MDMA group was much greater compared to the typical neuron in the SB/MDMA group (see Fig. 7). The mean (±SEM) magnitude of excitation (when the percent change from baseline for each excited unit was calculated for the entire post-MDMA period) for the VEH/MDMA and SB/MDMA groups was 1,323 (±597) and 424 (±75) % of baseline, respectively. Interestingly, the mean (±SEM) magnitude of inhibition in the VEH/MDMA group was also greater compared to the SB/MDMA group [30 (±7) and 70 (±7) % of baseline for VEH/MDMA and SB/MDMA groups, respectively]. Additionally, as Fig. 8 shows, a coefficient-of-variation analysis indicated significantly more variability in the magnitude of both MDMA-induced neuronal excitations and inhibitions in the VEH/MDMA group compared to the SB/MDMA group [t (28)=16.09, p<0.001 and t (28)=5.95, p<0.001 for excited and inhibited units, respectively].

Discussion

Consistent with our previous report (Ball et al. 2003), a locomotor-activating dose of MDMA excited a majority (58%) and inhibited a relatively small proportion (13%) of recorded striatal neurons in freely moving rats. We now extend these results by showing that prior administration of SR significantly attenuated MDMA-induced locomotion and blocked nearly all MDMA-induced striatal excitations. Conversely, prior administration of SB had no effect on the amount of MDMA-induced locomotor activity or the distribution of single-unit responses to MDMA. However, a coefficient-of-variation analysis indicated significantly less variability in the magnitude of both MDMA-induced neuronal excitations and inhibitions in rats that were pretreated with SB compared to VEH. It appears therefore that both 5-HT_{2A} and 5-$HT_{2C/B}$ receptors regulate the striatal response to MDMA, albeit in different ways.

Because the activity of striatal neurons changes dramatically when tested under conditions of immobilization or general anesthesia (Rebec et al. 1991; Warenycia and

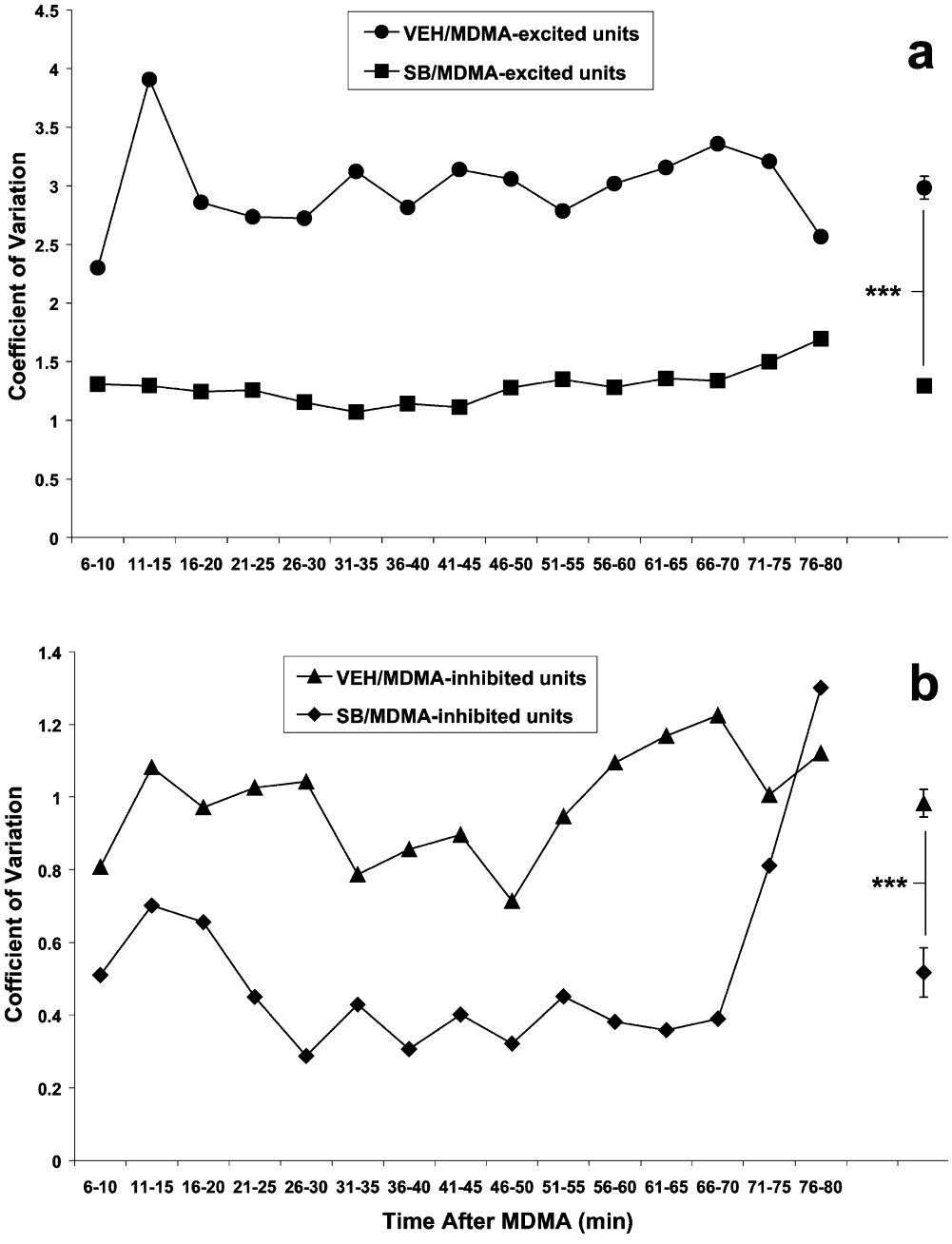

Fig. 8 Results of coefficient-of-variation analysis for excited (**a**) and inhibited (**b**) units in the VEH/MDMA and SB/MDMA groups across entire post-MDMA period. Data points to the far right indicate the mean (±SEM) of all data points in the corresponding category; points without error bars indicate the SEM is too small to illustrate. *Asterisks* indicate a significant difference in coefficient of variation, $p<0.001$

McKenzie 1984; West 1998), neurobehavioral relationships are best characterized when neuronal activity is examined in a behavioral context. Although the activation of striatal cells could represent a behavioral feedback effect, rather than a direct effect of MDMA in the striatum, several lines of evidence argue against this possibility. First, intrastriatal infusions of AMPH have been shown to change striatal neuronal activity well before the onset of behavioral activation (Wang and Rebec 1993). Also, when pre- and post-AMPH behaviors are "clamped" or held constant by analyzing neuronal activity only during behaviors matched for both form and intensity (Deadwyler 1986), AMPH still activates striatal cells (Haracz et al. 1993, 1998). We used a form of behavioral clamping in the present study and showed that locomotor activity following MDMA administration was associated with significantly faster firing rates relative to firing rates during locomotor activity prior to MDMA administration. Previously, we compared pre- and post-MDMA neuronal firing rates expressed during periods of matched locomotion and found that most units still showed MDMA-induced changes in firing rate relative to predrug locomotion (Ball et al. 2003). Thus, although behavioral clamping cannot rule out a relationship between neuronal activity and sensory events or covert behavioral processes, it appears that the effects of stimulants, including MDMA, on striatal neurons are not solely the result of behavioral feedback, but instead indicate a primary action of these drugs.

In contrast to systemically applied AMPH, iontophoretically applied AMPH in striatum inhibits the majority of

units in freely moving rats (Kiyatkin and Rebec 1997). Similarly, inhibitions predominate in dorsal and ventral striatum when MDMA is iontophoretically applied to these areas in anesthetized rats (Obradovic et al. 1996, 1998; White et al. 1994, 1995, 1996). Because iontophoretic application of drugs results in a very localized effect, these collective results suggest that the activation of one or more areas outside striatum is necessary for drug-induced striatal excitations. Support for this idea comes from studies showing that cortical ablation attenuates striatal single-unit excitations in response to systemically applied AMPH in freely moving rats (Tschanz et al. 1991, 1994). Thus, it appears that input from glutamatergic corticostriatal afferents is critical to the excitatory effect of AMPH, and possibly MDMA, on striatal neurons.

The involvement of 5-HT_2 receptors in the striatal neuronal response to MDMA was first suggested by Obradovic et al. (1996), who found that the 5-$HT_{2A/C}$ antagonist ketanserin attenuated the effect of MDMA on glutamate-evoked firing in nucleus accumbens core, an area anatomically and neurochemically similar to dorsal striatum (Heimer et al. 1991; Zahm and Heimer 1993). Using more selective antagonists, we found evidence that 5-HT_{2A} and $5HT_{2C/B}$ receptors play differential roles in both MDMA-induced neuronal activity and locomotor activation. Whereas SB had no effect on the amount of MDMA-induced locomotion, SR significantly attenuated the locomotor response to MDMA. At the neuronal level, the distribution of unit responses in the SB/MDMA group was indistinguishable from the VEH/MDMA group. In contrast, SR blocked nearly all MDMA-induced excitations and resulted in significantly more inhibitions compared to either the VEH/MDMA or SB/MDMA groups. These behavioral and electrophysiological data are consistent with a differential role for 5-HT_{2A} and 5-$HT_{2C/B}$ receptors in both the striatal and behavioral effects of MDMA.

Our finding that SR attenuated MDMA-induced locomotor activation is consistent with reports that $5HT_{2A}$ receptor activation is necessary for the full expression of MDMA-induced locomotion (Bankson and Cunningham 2002; Fletcher et al. 2002; Kehne et al. 1996). The role of 5-$HT_{2C/B}$ receptors, however, may be more difficult to characterize. Previous studies, for example, reported an enhancement of MDMA-induced locomotion following treatment with SB (Bankson and Cunningham 2002; Fletcher et al. 2002), whereas we did not observe this potentiation after SB pretreatment. Several methodological differences between our study and the above studies, such as methods of behavioral scoring, experimental design, and dosages of MDMA could potentially contribute to the different results. As regards this latter difference, it is possible that our dose of 5 mg/kg MDMA resulted in a ceiling effect that precluded SB from further potentiating MDMA-induced locomotion. This possibility is unlikely, however, because several groups have reported a greater magnitude of MDMA-induced locomotor activation when doses were increased from 5 mg/kg to a higher dose (Gold et al. 1988, 1989; Kehne et al. 1996; McNamara et al. 1995; Spanos and Yamamoto 1989). It is noteworthy that this dose is not neurotoxic to 5-HT neurons in rats (Fone et al. 2002; Kalivas et al. 1998; O'Shea et al. 1998; Slikker et al. 1989) and is within or close to the range of doses used by humans (Cole et al. 2002). In any case, our observation that SR attenuated MDMA-induced locomotion while SB had no effect on locomotion further supports data indicating that 5-HT_{2A} and 5-$HT_{2C/B}$ receptors play differential roles in MDMA-induced locomotor activation.

Although the proportions of excited, inhibited, and nonresponsive units in the SB/MDMA group were nearly identical to those observed in the VEH/MDMA group, two important electrophysiological differences were noted: (1) a coefficient of variation analysis revealed significantly more variability in the magnitude of both MDMA-induced neuronal excitations and inhibitions following pretreatment with VEH compared to SB, and (2) the overall magnitude of these excitations and inhibitions was greater in the VEH/MDMA group compared to the SB/MDMA group. These differences are interesting because we found no differences in the amount of locomotor activation between the VEH/MDMA and SB/MDMA groups. Thus, 5-$HT_{2C/B}$ receptor antagonism in some ways alters the striatal response to MDMA, but this change is not apparent in the behavioral response. These findings may have interesting implications regarding the nature of striatal control over motor behavior. Our electrophysiological results are consistent with the possibility that the overall magnitude of excitations and inhibitions in a population of striatal cells, as well as the amount of variability between individual cells in the population, are both variables that can influence the ultimate amount of behavioral output (Rebec 1998). According to our results, 5-$HT_{2C/B}$ receptors may play a role in modulating these variables, although the exact nature of this role is not known. In light of these findings, a more detailed analysis of behavior in response to MDMA combined with 5-$HT_{2C/B}$ receptor manipulations may be warranted.

Because 5-HT receptors modulate basal, as well as stimulant-induced, DA transmission (Gobert et al. 2000; Lucas and Spampinato 2000; Ng et al. 1999; Parsons et al. 1999; Porras et al. 2002; Schmidt et al. 1992), the extent to which 5-HT receptor activation directly controls MDMA-induced locomotion is an issue that has not been fully elucidated. Although the unique pattern of MDMA-induced locomotion likely results from complex mechanisms, several lines of converging evidence suggest that 5-HT control over MDMA-induced locomotion is largely due to modulation of the DA system. First, selective 5-HT release by fenfluramine causes hypolocomotion or no change in locomotion (Aulakh et al. 1988; Bankson and Cunningham 2002; Ziance et al. 1972), even when combined with an antagonist that blocks 5-$HT_{2C/B}$ receptors (Bankson and Cunningham 2002). The selective serotonin uptake inhibitor fluoxetine attenuates MDMA-induced 5-HT release (Gudelsky and Nash 1996; Hekmatpanah and Peroutka 1990; McKenna et al. 1991) and MDMA-induced locomotion (Callaway et al. 1990); however, fluoxetine also attenuates in vivo MDMA-induced DA release in striatum (Gudelsky and Nash 1996; Koch and Galloway 1997). There is evidence that this 5-HT-sensitive increase in

MDMA-induced striatal DA release may be mediated by 5-HT_2 receptors in the striatum and substantia nigra that ultimately influence GABA neurons in the substantia nigra (Yamamoto et al. 1995). Second, MDMA shares many commonalities with its parent drug, AMPH, a drug whose psychomotor stimulant effects are mediated by DA mechanisms (Segal and Kuczenski 1994; Seiden et al. 1993). It is evident that DA, acting at both D_1 and D_2 receptors, is necessary for the normal expression of both AMPH- and MDMA-induced locomotor activity (Ball et al. 2003; Bubar et al. 2004; Daniela et al. 2004; Gold et al. 1989; Kehne et al. 1996; Rosa-Kenig et al. 1993). Blockade of 5-HT_{2A} receptors attenuates both AMPH- and MDMA-induced locomotor activity (present results; Bankson and Cunningham 2002; Fletcher et al. 2002; Kehne et al. 1996; Moser et al. 1996), as well as in vivo AMPH- and MDMA-induced striatal DA release (Porras et al. 2002; Schmidt et al. 1992). This latter effect may be due to 5-HT_{2A} receptor regulation of DA synthesis (Schmidt et al. 1992). Both AMPH and MDMA have a predominantly excitatory effect on striatal single-unit activity in freely moving rats (present results; Ball et al. 2003; Haracz et al. 1989, 1993; Rebec et al. 1991; West et al. 1997), and this effect is dependent upon DA receptor activation (Ball et al. 2003; Haracz et al. 1993; Rebec et al. 1991; Rosa-Kenig et al. 1993; Wang and Rebec 1993). In addition, the effect of SR on MDMA-induced behavior and striatal single-unit electrophysiology in the present study is remarkably similar to what was observed after the DA D_2 receptor antagonist, eticlopride, was combined with MDMA administration (Ball et al. 2003). Thus, blockade of either DA D_2 or 5-HT_{2A} receptors significantly attenuates MDMA-induced locomotion for a full 80 min and abolishes nearly all MDMA-induced striatal excitations. Finally, as noted above, we found that SR attenuated MDMA-induced striatal and behavioral activation, whereas SB had no effect on the amount of MDMA-induced locomotion or the distribution of single-unit responses. This pattern of results suggests that changes in DA efflux may be primarily responsible for this differential behavioral effect. Consistent with this view, Porras et al. (2002) showed that at doses similar to those used in the present study, SR, but not SB, significantly reduced AMPH-induced DA release in the striatum and nucleus accumbens. It appears therefore that the ability of 5-HT receptors to control MDMA-induced locomotor activity, and perhaps striatal activity, may be due in large part to modulation of DA transmission.

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