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5-HT_2 Receptor Antagonism Reduces Hyperactivity Induced by Amphetamine, Cocaine, and MK-801 But Not D_1 Agonist C-APB

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O'NEILL, M. F., C. L. HERON-MAXWELL AND G. SHAW. *5-HT_2 receptor antagonism reduces hyperactivity induced by amphetamine, cocaine, and MK-801 but not D_1 agonist C-APB*. PHARMACOL BIOCHEM BEHAV **63**(2) 237–243, 1999.—The hyperlocomotion induced by the noncompetitive NMDA antagonist MK-801 (0.3 mg/kg SC) in mice was attenuated by the nonselective 5-HT_2 antagonist ritanserin (0.12 and 0.25 mg/kg SC) and by the 5-HT_{2A} selective antagonist MDL100907 (0.05 and 0.1 mg/kg SC). SB242084 (0.25–1.0 mg/kg), a selective 5-HT_{2C} antagonist, had no effect on MK-801–induced hyperactivity. These same doses of ritanserin and MDL100907 reduced the hyperactivity induced by cocaine (10 mg/kg). Amphetamine (2.5 mg/kg SC) induced hyperlocomotion that was also attenuated by ritanserin (0.06–0.25 mg/kg SC). The hyperlocomotion induced by the D_1 agonist C-APB (1.0 mg/kg) is not altered by pretreatment with ritanserin or MDL100907. This suggests that compounds that increase locomotor activity via indirectly increasing dopaminergic activity (either by increased release or blockade of reuptake) require the activation of a 5-HT_{2A} receptor. Activity of compounds that act directly at the postsynaptic dopamine receptors such as C-APB is not dependent on such a mechanism. This suggests a selective involvement of 5-HT_{2A} receptors but not 5-HT_{2C} receptors in the mediation of the behavioral effects of compounds that increase synaptic concentration of dopamine but not directly acting agonists. This implies that the 5-HT_{2A} receptors modulate elevation of extracellular dopamine, not the postsynaptic sensitivity of dopamine neurons. © 1999 Elsevier Science Inc.

Psychostimulants 5-HT_2 Hyperlocomotion C-APB D_1 agonist MK-801

CLOZAPINE was the first compound to treat schizophrenia that had a significantly reduced extrapyramidal side effect (EPS) profile and at the same time showed efficacy in the treatment of negative symptoms such as social withdrawal [see (9) for review]. Clozapine has a broad range of pharmacological actions (1,7), and much effort has been expended in identifying which aspect or aspects of its pharmacology are responsible for its effects in schizophrenia. Clozapine has greater affinity for 5-HT_2 receptors than it has for either D_1 or D_2 dopamine receptors (1). Schizophrenic symptoms have hitherto been regarded as the outcome of a dysregulation of dopaminergic systems (32,33). With the identification of the additional activity of clozapine at these receptors 5-HT_2 antagonism was identified as a potentially critical component of the profile of an atypical antipsychotic (22). A new generation of antipsychotics such as olanzapine, risperidone, and sertindole have affinity for 5-HT_2 receptors equal or greater than their affinity for dopamine receptors, and all have been reported to have reduced EPS and increased efficacy in the treatment of negative symptoms (20,37,38). It is not clear, however, how 5-HT_2 receptor antagonism contributes to the improved efficacy or more favorable profile of the new generation of antipsychotics (31).

It would appear that tonic activation of 5-HT_2 receptors plays an enabling role in the maintenance of enhanced dopamine release (29). Thus, blockade of this receptor may

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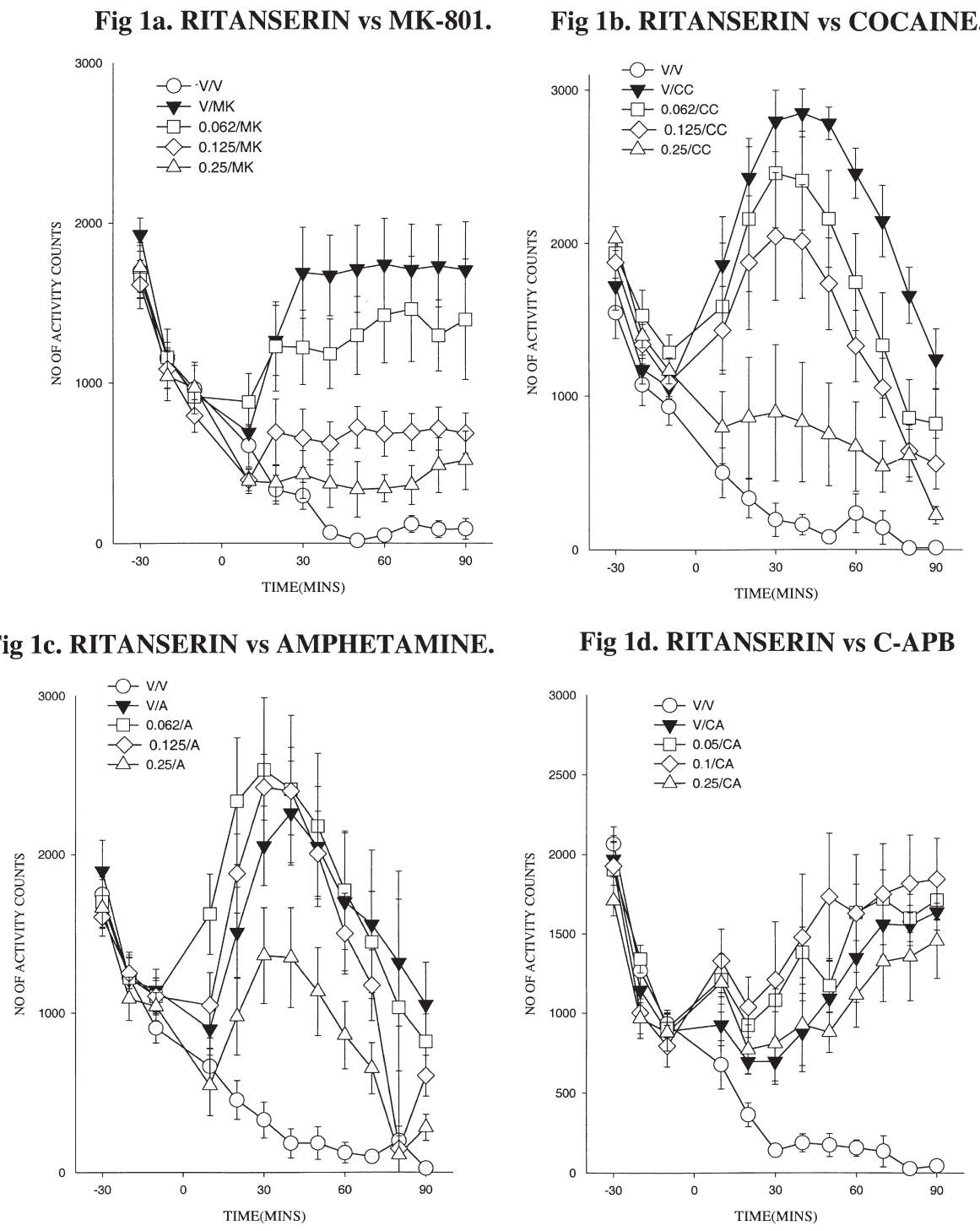

FIG. 1. Effect of ritanserin on locomotor stimulant compounds. X-axis shows time posttreatment, Y-axis shows mean number of photocell interrupts per group and SEM. Data are mean number of photocell interrupts for each group at each time point and SEM (n = 6 pairs). (a) Ritanserin vs. MK-801 (0.3 mg/kg). V/V—vehicle/vehicle, V/MK—vehicle/MK-801. 0.06/MK—ritanserin 0.06 mg/kg vs. MK-801, 0.12/MK—ritanserin 0.12 mg/kg vs. MK-801, 0.25/MK—ritanserin 0.25 mg/kg vs. MK-801. (b) Ritanserin vs. cocaine (10 mg/kg). V/V—vehicle/vehicle, V/CC—vehicle/cocaine, 0.062/CC—ritanserin 0.062 mg/kg vs. cocaine, 0.125/CC—ritanserin 0.125 mg/kg vs. cocaine, 0.25/CC—ritanserin 0.25 mg/kg vs. cocaine. (c) Ritanserin vs. amphetamine (2.5 mg/kg); V/V—vehicle/vehicle, V/CC—vehicle/amphetamine, 0.062/CC—ritanserin 0.062 mg/kg vs. amphetamine, 0.125/CC—ritanserin 0.125 mg/kg vs. amphetamine, 0.25/CC—ritanserin 0.25 mg/kg vs. amphetamine. (d) Ritanserin vs. C-APB (1.0 mg/kg); V/V—vehicle/vehicle, V/CC—vehicle/C-APB, 0.062/CC—ritanserin 0.062 mg/kg vs. C-APB, 0.125/CC—ritanserin 0.125 mg/kg vs. C-APB, 0.25/CC—ritanserin 0.25 mg/kg vs. C-APB.

contribute to "normalizing" levels of dopamine release. Blockade of 5-HT_2 receptors with the selective 5-HT_{2A} receptor antagonist MDL100907 attenuates dopamine efflux in the nucleus accumbens induced by the noncompetitive NMDA antagonist MK-801 (30). This finding is of particular interest in that noncompetitive NMDA antagonists such as phencyclidine and ketamine induce symptoms very similar to schizophrenia in humans (14). Unlike cocaine and amphetamine, phencyclidine also mimics the negative symptoms of schizophrenia, inducing social withdrawal, hostility, and fearfulness. Antipsychotics such as haloperidol and pimozide also successfully control the effects of PCP intoxication in humans (11).

NMDA antagonists such as PCP and MK-801 induce hyperactivity and characteristic stereotyped behaviors in rodents (5). Some of the behavioral effects of PCP and MK-801 in mice, most notably the hyperlocomotion, are reversed by pretreatment with both typical and atypical antipsychotic compounds [e.g., (6,10,12)].

It has been suggested that psychostimulant compounds are acting via a common dopaminergic pathway (40). If this is the case, then 5-HT_2 receptor blockade should equally antagonize other stimulant compounds such as cocaine and amphetamine. Preclinical data on this point has been equivocal. It has been demonstrated that 5-HT_2 receptor antagonists can attenuate the locomotor activity induced by the noncompetitive NMDA antagonists phencyclidine (PCP) (12) and MK-801 (2,27). It has also been demonstrated that MDL100907 can attenuate the hyperactivity induced by a range of stimulants including MK-801, atropine, and the dopamine uptake inhibitor GBR12909 (2,34). It has been shown that MDL100907 reverses the hyperactivity induced by amphetamine in rats, but the nonselective 5-HT_2 antagonist ritanserin failed to do produce a similar reversal (23). It is often difficult to compare the effects across different studies, as different stimulants and antagonists have been used. Furthermore, different experimental protocols and test species have been employed in the various studies, all of which can affect the outcome. We set out to further evaluate the role of 5-HT receptor subtypes in the mediation of hyperactivity by examining the effect of ritanserin as well as MDL 100907 on the hyperactivity induced by cocaine and amphetamine, and to compare it to their effects on MK-801-induced hyperactivity all under the same test conditions.

Furthermore, if 5-HT_2 receptors presynaptically modulate dopamine release, then 5-HT_2 receptor antagonism should not alter the response to a directly acting postsynaptic agonist. D_1 dopamine receptors are believed to exclusively located postsynaptically (4). Therefore, we also examined the effect of ritanserin on the selective dopamine D_1 agonist C-APB (SKF82958), which has been shown to act as a full agonist at D_1 receptors (25).

Previous studies in our labs under the same conditions employed in the present study (28) have shown that 0.3 mg/kg of MK-801, 10 mg/kg of cocaine, 2.5 mg/kg amphetamine, and 1.0 mg/kg C-APB all induced a robust increase in locomotor behavior, and these doses were used in the antagonist experiments in the current study.

METHOD

Animals

Female BKTO mice (25–30 g, Bantin and Kingman, Hull, UK) were housed in groups of 15 for at least 1 week following delivery. Animals were kept under standard conditions with a 12-h light cycle (lights on 0700 to 1900 h). Animals had ad lib

TABLE 1

EFFECT OF RITANSERIN AND MDL100907 ON LOCOMOTOR STIMULATION INDUCED BY MK-801, COCAINE, AMPHETAMINE, AND C-APB IN MICE

	MK-801 0.3 mg/kg	COCAINE 10 mg/kg	AMPH 2.5 mg/kg	C-APB 1.0 mg/kg
Ritanserin				
				(rit = 0.05–0.25)
V/V	1656 ± 238	1680 ± 577	2257 ± 503	1906 ± 256
V/T	13901 ± 2021‡	20229 ± 1138‡	14387 ± 2483‡	10388 ± 1195‡
0.062/T	11370 ± 2172‡	15524 ± 2571‡	16149 ± 3026‡	12426 ± 438‡
0.125/T	3835 ± 1051*#	12671 ± 2146‡§	13888 ± 1654‡§	13815 ± 2679‡
0.25/T	3590 ± 1094#	6177 ± 2321#	7640 ± 1730‡#	9822 ± 1704‡
MDL100907				
V/V	1795 ± 220	2168 ± 326	2817 ± 809	1974 ± 602
V/T	16362 ± 2660‡	16437 ± 1138‡	19419 ± 959‡	14670 ± 923‡
0.025/T	10202 ± 1203‡§	6320 ± 2028#	11942 ± 1428‡#	14237 ± 1135‡
0.05/T	6750 ± 1893*#	9859 ± 2411†§	11415 ± 1631‡#	15320 ± 1451‡
0.1T	7857 ± 967†#	5015 ± 1708#	13101 ± 1480‡§	14630 ± 1104‡
SB 242084				
V/V	3279 ± 2047			
V/T	17234 ± 2156‡			
0.25/T	19304 ± 1937‡			
0.5/T	18207 ± 2415‡			
1.0/T	21036 ± 2120‡			

Data show mean number of photocell interrupts with sem for each group ($n \geq 6$) for the 90 min test period. Significant differences determined by least square means test following significant ANOVA.

* $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ vs. vehicle control.

§ $p < 0.01$, # $p < 0.001$ vs. vehicle/treatment (T).

Fig 2a. MDL100907 vs MK-801.

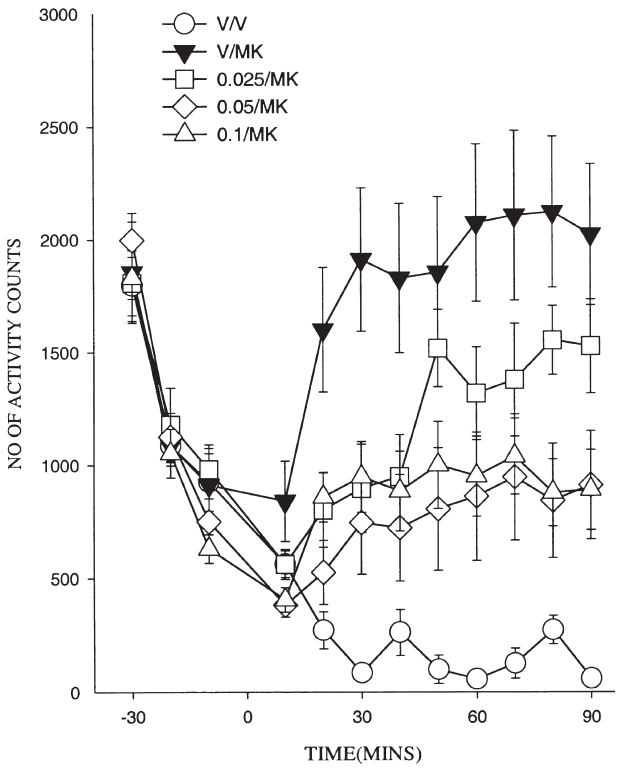

Fig 2b. MDL100907 vs COCAINE.

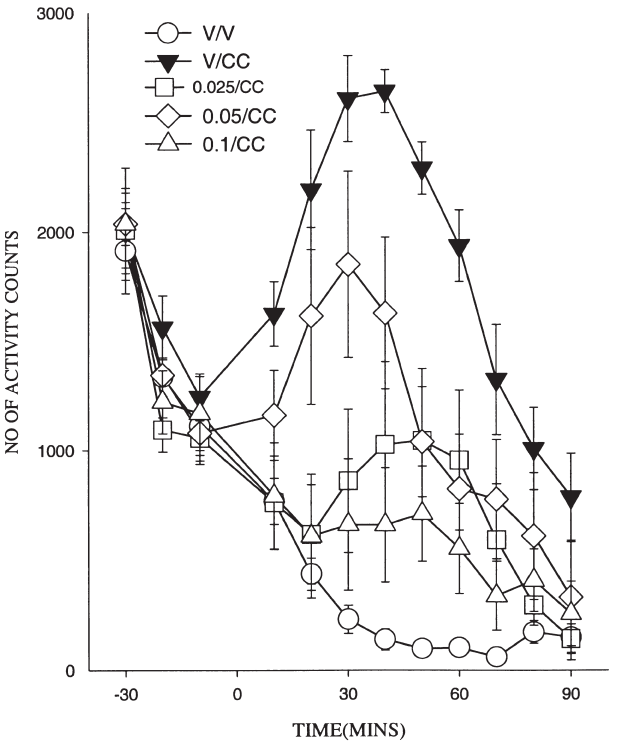

Fig 2c. MDL100907 vs C-APB.

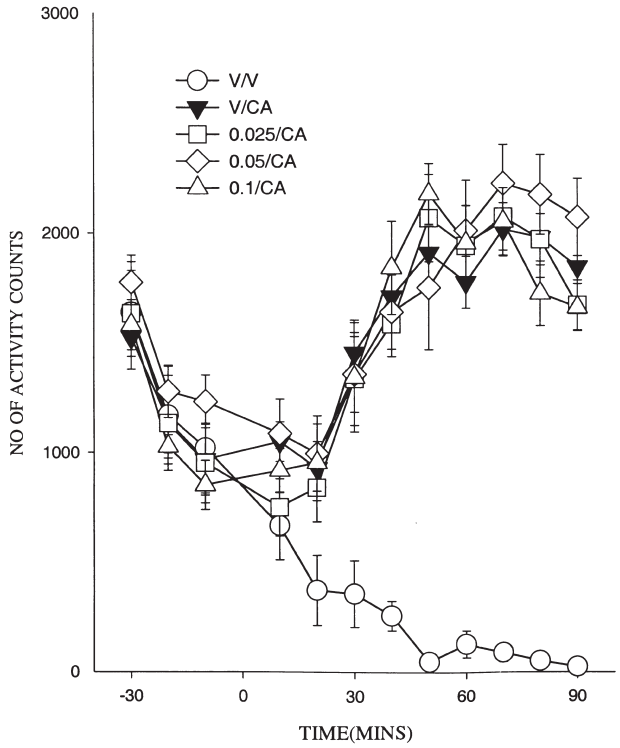

FIG. 2. Effect of MDL100907 vs. locomotor stimulant compounds. X-axis shows time posttreatment, Y-axis shows mean number of photocell interrupts. Data are mean number of photocell interrupts for each group at each time point and sem (n = 6 pairs). (a) MDL100907 vs. MK-801 (0.3 mg/kg); V/V—vehicle/vehicle, V/MK—vehicle/MK, 0.025/MK—MDL100907 0.025 vs. MK-801, 0.05/MK–MDL100907 0.05 mg/kg vs. MK-801, 0.1/MK—MDL100907 0.1 mg/kg vs. MK-801. (b) MDL100907 vs. cocaine (10 mg/kg); MDL100907 vs. cocaine; V/V—vehicle/vehicle, V/MK—vehicle/MK, 0.025/MK—MDL100907 0.025 vs. cocaine, 0.05/MK—MDL100907 0.05 mg/kg vs. cocaine, 0.1/MK—MDL100907 0.1 mg/kg vs. cocaine. (c) MDL100907 vs. C-APB (1.0 mg/kg); MDL100907 vs. C-APB; V/V—vehicle/vehicle, V/MK—vehicle/MK, 0.025/MK—MDL100907 0.025 vs. C-APB, 0.05/MK—MDL100907 0.05 mg/kg vs. C-APB, 0.1/MK—MDL100907 0.1 mg/kg vs. C-APB.

access to both food and water. Experiments were carried out between 1000 and 1700 h. All experiments were conducted under the conditions laid down in the UK Animal Scientific Procedures Act 1986.

Drugs

MK-801 (RBI) and cocaine (Sigma) were dissolved in distilled water. MDL100907 and SB242084 were synthesized at Lilly Research Labs. MDL 100907, SB242084, and ritanserin (generously supplied by Janssen Pharmaceuticals) were suspended in 25% beta-cyclodextrin and sonicated briefly to aid suspension. All doses were given subcutaneously (SC) in a volume of 10 ml/kg.

Apparatus

Locomotor activity was measured in clear Perspex boxes (30 × 30 × 30 cm) with a metal base covered with 2 cm of fine

sawdust. Each box had five equally spaced pairs of horizontal photocell beams, 3 cm above the sawdust. Each beam break was recorded as a photocell count. All of the boxes were connected to a Compaq PC, which recorded the number of photocell interrupts made in each cage for every minute of the test period.

Procedure

To minimize the variation among individuals, mice were tested in pairs in the locomotor activity boxes. Each pair received the same treatment, and the data used was the total number of activity counts per activity cage for the relevant time period. Animals were first injected with pretreatment and placed in pairs in the photocell cages where their activity was measured for a 30-min habituation period. When this time had elapsed, the animals were injected with the appropriate dose of compound or vehicle and then returned to the test cages. Recording was begun immediately, and activity was measured for 90 min postinjection. The Perspex cages allowed for continuous visual monitoring of the animals in addition to the automated measure of locomotor activity.

Statistical Analysis

The photocell counts for each locomotor activity caged were grouped into 10-min bins. The one-way ANOVAs were performed on the data for each 10-min bin and for the total number of activity counts for both the 30-min habituation period and the 90-min test period for each group. Post hoc least square means tests were used to test for intergroup differences following a significant ANOVA.

RESULTS

Ritanserin at doses had no effect on spontaneous activity (0.062–0.25 mg/kg) in the habituation period, $F(4, 31) = 0.2$, $p < 0.9$. Ritanserin did, however, dose dependently attenuate the significant increase in hyperlocomotion induced by MK-801 (0.3 mg/kg), $F(4, 29) = 12.1$, $p < 0.001$. This suppression of MK-801 was evident throughout the 90-min test period (Fig. 1a, Table 1). Post hoc tests following a significant treatment effect showed that the minimum effective dose (MinED) for the reversal of MK-801-induced activity was 0.125 mg/kg.

The same doses of ritanserin (0.062–0.25 mg/kg) significantly and dose dependently reversed the hyperlocomotor effects of cocaine (10 mg/kg) (Fig. 1b, Table 1), $F(4, 29) = 13.42$, $p < 0.001$. The same MinED of ritanserin (0.125 mg/kg) completely abolished the significant hyperactivity induced by amphetamine (2.5 mg/kg) (Fig. 1c, Table 1), $F(4, 31) = 7.84$, $p < 0.001$. Ritanserin (0.25 mg/kg) had no effect, however, on the hyperlocomotion induced by the selective dopamine D_1 agonist C-APB, $F(4, 29) = 7.5$, $p < 0.001$ (1 mg/kg) (Fig. 1d, Table 1).

The 5-HT$_{2A}$ selective antagonist MDL100907 (0.025–0.1 mg/kg) significantly attenuated the significant increase in locomotion induced by MK-801 (0.3 mg/kg), $F(4, 31) = 10.3$, $p < 0.0001$ (Fig. 2a, Table 1). MDL100907 had no effect on spontaneous activity in the habituation period at these doses, $F(4, 31) = 0.5$, $p < 0.7$. MDL100907 also significantly reversed the increase in locomotor activity induced by cocaine (10 mg/kg), $F(4, 31) = 12.5$, $p < 0.0001$ (Fig. 2b, Table 1). MDL 100907 significantly reversed to locomotor stimulation induced by amphetamine (2.5 mg/kg), $F(4, 31) = 18.2$, $p < 0.0001$. The locomotor stimulant effects of MK-801, cocaine, and amphetamine were only partly reduced by MDL100907, and increasing the doses did not induce a corresponding further suppression of the locomotor activation by the stimulants. None of the doses of MDL100907 that were active against the hyperactivity induced by either MK-801, cocaine, or amphetamine had any effect on the hyperactivity induced by C-APB (1.0 mg/kg), $F(4, 31) = 25.0$, $p < 0.0001$ (Fig. 2c, Table 1).

Spontaneous locomotor activity in the habituation period was also unaffected by the 5-HT$_{2C}$ antagonist SB242084, $F(4,31) = 1.8$, $p < 0.15$. This same compound (0.25–1.0 mg/kg) had no effect on the hyperlocomotor response induced by MK-801, $F(4, 31) = 10.45$, $p < 0.001$ (Fig. 3, Table 1).

DISCUSSION

Ritanserin significantly attenuated the locomotor response not only to MK-801 but also to cocaine and amphetamine. MDL100907 also significantly reduced activity when tested against the hyperlocomotion induced by MK-801 and cocaine. MDL100907 attenuated the effects of MK-801 and of cocaine

Fig 3. SB242084 vs MK801.

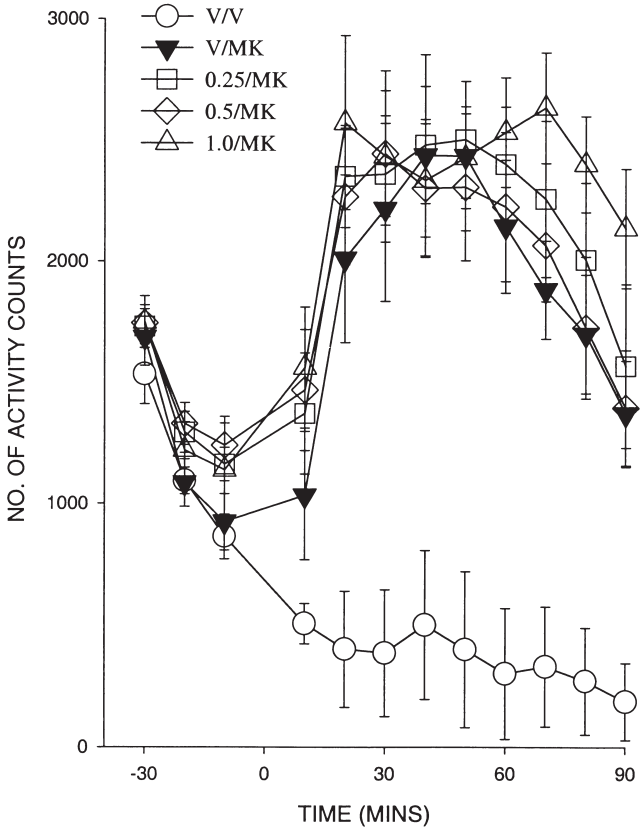

FIG. 3. SB242084 vs. MK-801; time course. X-axis shows time post-treatment, Y-axis shows mean number of photocell interrupts. Data are mean number of photocell interrupts for each group at each time point and sem ($n = 5$ pairs). SB242084 vs. MK-801; V/V—vehicle/vehicle, V/MK—vehicle/MK, 0.25/MK—SB242084 0.025 vs. MK-801, 0.5/MK—SB242084 0.05 mg/kg vs. MK-801, 1.0/MK—SB242084 1.0 mg/kg vs. MK-801.

in these tests at doses that did not alter spontaneous activity given alone. It has previously been shown that this compound has no intrinsic effect on locomotor activity at doses considerably in excess of those used in the present study (23) .

MDL100907 did not appear to produce a clearly dose-related inhibition of either MK-801 or cocaine-induced hyperlocomotion unlike ritanserin, which dose dependently reversed the effects of both stimulants. This may have been due to formulation or solubility issues as the compound formed a fine suspension in the β-cyclodextrin vehicle, which may not have been optimal for delivering increasing doses of the compound with increasing concentrations. Another possibility may derive from the fact that ritanserin and MDL100907 differ in their selectivity for 5-HT_2 receptor subtypes. Thus, while MDL100907 has a very high affinity for 5-HT_{2A} receptors, it is much less active at the 5-HT_{2B} and 5-HT_{2C} subtypes. Ritanserin, on the other hand, is almost equiactive at all subtypes (13). SB242084, a selective 5-HT_{2C} antagonist (17), did not significantly reduce the response to MK-801, suggesting, however, that 5-HT_{2C} receptors are not involved.

Selective blockade of 5-HT_{2A} receptors may only have reduced selective elements of the MK-801-induced behavioral syndrome. Nabeshima et al. (24) showed that ritanserin reduced the head twitches but failed to block the head weaving induced by PCP in mice. Direct observation showed, however, that no head weaving was induced by the dose of MK-801 (0.3 mg/kg) used in the present study. It is likely that the diverse neurochemical actions of MK-801 (19) resulting in an increase in locomotor activity involves several transmitters, only some of which are sensitive to 5-HT_{2A} modulation. It has been shown that large doses of MK-801 can induce hyperactivity even in monoamine-depleted animals, supporting the suggestion that other nonmonoamine systems may contribute to its behavioral response (3).

The attenuation of the locomotor activation induced by MK-801, cocaine, and amphetamine by the 5-HT_2 antagonists clearly implicates 5-HT_2 receptors in the mediation of the effects of these agents. MDL100907 blocks the outflow of dopamine induced by MK-801 in the nucleus accumbens but does not alter basal dopamine release (29). This suggests that activation of the 5-HT_2 receptor may also be a necessary condition for an increase in dopaminergic activation following an increase in synaptic concentration of dopamine. Thus, it would appear that when the 5-HT_{2A} receptor is blocked, the increase in dopamine release necessary for stimulant-induced hyperactivity is inhibited and the hyperactivity is attenuated. The results of the present study suggest that this is not just specific to MK-801–induced hyperactivity but also cocaine and amphetamine-induced hyperactivity are blocked by 5-HT_2 receptor antagonists. The effects of both are mediated via increased synaptic concentrations of dopamine. This is in accord with the finding that MDL 100907 significantly decreased the hyperactivity induced by MK-801, atropine, and the dopamine reuptake inhibitor GBR12909 (2).

It has also previously been demonstrated that MDL 100907 had no effect on apomorphine-induced stereotypies in rats (15). This may be interpreted as indicating that MDL100907 shows preferential blockade of the more accumbens-related locomotor responses to amphetamine over the striatally mediated apomorphine-induced stereotypies. This is based on the finding that stereotypies are predominantly striatally mediated, whereas locomotor hyperactivity is mediated by increased dopaminergic activity in the accumbens (16). C-APB is a selective dopamine D_1 agonist that acts via stimulation of postsynaptic D_1 receptors. In the present study, the hyperlocomotion induced by C-APB was also unaffected by pretreatment with ritanserin or with MDL100907. This may imply that the modulatory effect of 5-HT_2 receptors on dopamine-mediated hyperactivity is presynaptic, and is possibly regulating dopamine release rather than altering the postsynaptic response of dopaminergic neurons.

Previous studies in our lab have shown that dopaminergic antagonists such as haloperidol, SCH23390, and raclopride suppress the effects of MK-801 only at doses that also suppress spontaneous locomotor activity (28). In the present study, it has been shown that 5-HT_2 antagonists, MDL100907 and ritanserin, can reduce MK-801-induced hyperactivity without altering spontaneous locomotor activity. This spontaneous exploratory activity has been ascribed to increased dopamine release in response to the novel of experimental stimuli [see (39) for review]. The fact that this activity is unaltered while the activity induced by the cocaine, amphetamine, and MK-801 was significantly reduced, implies that they may act via different dopaminergic mechanisms. Thus, the "normal" increase in dopamine release induced by exposure to a novel environment and the associated increase in activity may not involve the 5-HT_{2A} receptor that acts in a permissive role for the activation induced by the psychostimulant compounds. This is consistent with the proposition that 5-HT_2 receptors are not activated under "normal" tonic conditions (18).

The findings of the current study may question the hypothesis that the locomotor stimulation induced by the NMDA antagonist MK-801 may represent and animal model of PCP intoxication and even psychosis in humans (14). PCP toxicity in humans has been reported to respond to dopaminergic antagonists such as haloperidol and pimozide (11). Furthermore, the clinical evidence for 5-HT_2 antagonists being effective as antipsychotics is slight (35). In the only clinical study published so far with MDL100907, the selective 5-HT_{2A} antagonist showed no significant effect on positive symptoms and a nondose-dependent attenuation of negative symptoms in schizophrenics (26). While some studies report an improvement in mood and the affective aspects of schizophrenia with ritanserin treatment (8), no reports are available suggesting an improvement in primary positive symptoms, and one report even showed an exacerbation of psychotic symptoms (36). It has been shown that the reversal of MK-801-induced hyperactivity by MDL100907 is, in turn, reversed by ritanserin (21). This suggests that ritanserin may have some agonist efficacy. This may partly explain why ritanserin has been ineffective or even propsychotic in clinical trials. Only further clinical evaluation of selective 5-HT_{2A} antagonists will ascertain if blockade of MK-801-induced hyperactivity has any construct validity as a model of schizophrenia.

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