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WAY 100135, an Antagonist of 5-HT1A Serotonin Receptors, Attenuates Psychotomimetic Effects of MK-801

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In the present study, we investigated whether the antagonist of 5-HT1A receptors, WAY 100135, was capable of modifying the psychostimulant and psychotomimetic effects of MK-801, a non-competitive antagonist of NMDA receptors. It was found that: 1) WAY 100135 (10 and 20 mg/kg, but not 1.25, 2.5, and 5 mg/kg) transiently, in a dose dependent manner, attenuated the locomotor stimulant effects of MK-801 (0.4 mg/kg). Given alone, WAY 100135 had no effect on the locomotor activity of rats; 2) WAY 100135 (1.25 and 2.5 mg/kg, but not 10 or 20 mg/kg), attenuated or abolished the disruptive effects of MK-801 on the sensorimotor gating measured in a prepulse-induced inhibition of the acoustic startle response paradigm. WAY 100135 in all tested doses had no effect on the sensorimotor gating or amplitude of the acoustic startle response; 3) WAY 100135 (1.25, 2.5 mg/kg, but not 5 mg/kg) attenuated the detrimental effects of MK-801 on working memory and selective attention, measured in a delayed alternation task. Again, given alone, WAY 100135 did not influence the behavior of rats in that experimental paradigm; and 4) MK-801 (0.4 mg/kg) had no effect on the 5-HT1A receptor mRNA level in rat hippocampus, measured 2 and 24 hours after MK-801 administration. These data indicate that 5-HT1A receptors might be involved in the psychotomimetic effects of non-competitive NMDA receptor antagonists. In addition, 5-HT1A serotonin receptor antagonists and partial agonists may have potential antipsychotic properties.

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Non-competitive antagonists of NMDA receptors such as phencyclidine (PCP) or ketamine are known for their strong, frequently neuroleptic-resistant psychotomimetic effects in humans (Javitt and Zukin 1991). These clinical effects, as well as evidence suggesting the involvement of NMDA receptors in the pathophysiology of schizophrenia (Carlsson et al. 1999; Harrison 1999; Wachtel and Turski 1990), support the experimental modeling of psychoses by administration of non-competitive NMDA receptor antagonists (Jentsch and Roth 1999). In this respect, MK-801 seems to be of special interest in experimental pharmacology. It belongs to a class of non-competitive NMDA receptor antagonists (Seeburg 1993; Lodge and Johnson 1990; Willetts et al. 1990) and MK-801 seems to be highly specific to the PCP binding site located in the ion channel of the NMDA receptor complex (Lodge and Johnson 1990; Seeburg 1993).

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As a functional congener of PCP, MK-801 evokes robust psychostimulant and psychotomimetic effects such as enhancement of locomotor activity (Carlsson 1993; Maj et al. 1991), impairment of sensorimotor gating (Mansbach and Geyer 1989; Wędzony et al. 1994), and detrimental effects on spatial working memory (Verma and Moghaddam 1996). Although it is generally agreed that the psychostimulant and psychotomimetic effects of PCP, ketamine, and MK-801 are initiated by blockade of the NMDA receptor ion channel complex, the neuronal pathways or neurotransmitter systems involved in the propagation of the psychotomimetic effects are not precisely known (Bakshi and Geyer 1998). Moreover, the apparent lack of chemical compounds which might directly abolish the pharmacological blockade of these NMDA receptors (Lodge and Johnson 1990; Willetts et al. 1990), and prevent impairments of their function during the course of schizophrenia (Harrison 1999) justifies attempts to define neuroanatomical/neurochemical systems responsible for the propagation of the effects of non-competitive NMDA receptors.

Apart from the dopaminergic system (Jentsch and Roth 1999), traditionally linked with psychotomimetic effects of non-competitive antagonists of NMDA receptors, and the noradrenergic system [currently under investigation (Bakshi and Geyer 1998, 1999; Jentsch et al. 1998)], considerable interest has been focused on serotonin and its receptors (Geyer 1998). It has been shown, for example, that MK-801 increases serotonin release (Whitton et al. 1992) and influences serotonin turnover (Loscher et al. 1991; Wędzony et al. 1997). Moreover, the psychostimulant and psychotomimetic effects of MK-801 and PCP are attenuated by specific antagonists of 5-HT2A receptors (Schmidt and Fadayel 1996; Varty et al. 1999; Varty and Higgins 1995).

Apart from 5-HT2A receptors, a growing number of studies indicate that MK-801 may also influence other serotonin receptors; for example, it increases mRNA of 5-HT6 and 5-HT7 receptors (Healy and Meador-Woodruff 1999). Moreover, the increased density of 5-HT1A receptors after a single administration of MK-801 has been reported in one of our recent studies (Wędzony et al. 1997). The possible involvement of 5-HT1A receptors in the psychotomimetic effects of NMDA receptor antagonists is further supported by observations that the 5-HT1A receptor antagonist WAY 100135 is capable of abolishing the psychostimulant effects of MK-801 (Loscher and Honack 1992, 1993).

In the present study, we attempted to find out whether WAY 100135 was able to influence the psychotomimetic effects of MK-801 that mimic the cognitive deficits in schizophrenia. The first series of experiments investigated, the impact of WAY 100135 on the locomotor hyperactivity induced by MK-801, in order to link our present experiments with the previous findings of Loscher and Honack (1992, 1993), and to analyze the time-course of interaction between WAY 100135 and MK-801.

In the second set of experiments, we investigated whether WAY 100135 can influence the detrimental effects of MK-801 on sensorimotor gating measured as prepulse induced inhibition of the acoustic startle response (PPI). Non-competitive antagonists of NMDA receptors evoke strong impairments of PPI (Mansbach and Geyer 1989; Wędzony et al. 1994) which are also observed in schizophrenic patients (Cadenhead et al. 1997). Due to similarities between clinically observed impairments of sensorimotor gating and the effects of non-competitive antagonist of NMDA receptors, PPI is widely used as an experimental model with high face and predictive validity for novel antipsychotic drugs.

In the third set of experiments, we investigated the impact of WAY 100135 on the MK-801-induced impairment of spatial working memory in rats (Goldman-Rakic 1996). These studies were initiated on the basis of two sets of findings. First, an abnormal function of the prefrontal cortex in schizophrenic patients accompanied their poor performance in working memory tests (Stevens et al. 1998). Second, non-competitive antagonists of the NMDA receptors evoked robust deficits in spatial working memory (Verma and Moghaddam 1996; Adams and Moghaddam 1998), modeling the cognitive deficits typical of schizophrenia (Stevens et al. 1998).

Finally, the impact of MK-801 on the level of 5-HT1A receptor mRNA was assessed. This experiment was based on our earlier findings that a single dose of MK-801 increased the number of 5-HT1A receptor binding sites in various regions of rat brain (Wędzony et al. 1997). Thus, it was of interest to corroborate and further examine the already obtained data, and to determine whether the above-mentioned receptor changes were generated at a transcription level.

MATERIALS AND METHODS

Animals

All experiments were carried out on male Wistar rats (Gorzkowska-Breeder , Warsaw, Poland) weighing 200–250 g at the time of the experiments. After delivery, the rats were habituated to the experimental room for at least 10 days, and were kept in groups of six to a cage at a constant temperature (22°C ± 2) and on an artificial light/dark cycle (12/12h; light on from 7 A.M. to 7 P.M.), with free access to tap water and laboratory chow.

Experiments on delayed alternation were an exception from that rule, since rats—though kept in the same experimental environment—had limited access to laboratory chow. They received food once daily (15 g per

day) directly after training or testing, whereas water was available *ad libitum.* The experiments were performed between 9.00 A.M. and 5.00 P.M.

Measurement of the Locomotor Activity

The locomotor activity of rats was recorded individually for each animal in Opto-Varimex cages (Columbus Instruments, OH), linked on-line to an IBM-PC compatible computer. Each cage (43–44 cm) was equipped with 15 infrared emitters, located on the x and y axes, and with an equivalent amount of receivers located on the opposite walls of the cage. The locomotor activity of rats was analyzed using Auto-Track software (Columbus Instruments). The locomotor activity was defined as a trespass of three consecutive photo-beams, while other movements (e.g., repeated interruption of the same photo-beams) were regarded as stereotypy-like movements (data not given). The above procedure differentiated between the locomotor activity associated with horizontal locomotion and stereotypy-like movements which were concomitant with the increased locomotion after non-competitive NMDA receptor antagonists (Wędzony et al. 1996a).

The locomotor activity of rats was measured throughout a session lasting 160 min, during which—after 30-min habituation—the rats were injected with a respective dose of WAY 100135; later, after another 10 min, they were injected with MK-801 (0.4 mg/kg).

Prepulse-Induced Inhibition of Acoustic Startle Response

The startle apparatus (Columbus Instruments) consisted of three plastic, transparent cages, equipped with a moveable floor attached to a sensor which recorded movements of the floor. Since the sensors were sensitive to vertical movements only (up- and down-movements of an animal), horizontal movements of animals resulting, e.g., from the locomotor activity, could not be recorded with an apparatus of that type. A loudspeaker was suspended above each cage and the cages were placed in sound-proof cabinets. Transient force, resulting form up- and down-movements of the floor evoked by a startle reaction to acoustic stimuli, was recorded with a PC computer during a recording window of 200 ms, measured from the onset of the acoustic stimuli, and was then digitalized and stored in the computer for further evaluation. The amplitude of the startle response was defined as a difference between the maximum force detected during a recording window and the force measured immediately before the stimulus onset. The threshold level was set at 10 g, so that responses exceeding a force of 10 g would activate the automatic peak detection software. The threshold set at 10 g allowed a correct evaluation of the maximum response in all the animals tested.

In experiments dealing with the impact of WAY 100135 on detrimental effects of MK-801 on the sensorimotor gating, measured as prepulse-induced inhibition of the acoustic startle response, the rats were confronted—after habituation lasting 5 min (background white noise, 65 dB)—with two types of acoustic stimuli (pure acoustic tones, 4000 Hz): pulse alone trials—when acoustic stimuli of 120 dB were applied (duration of a acoustic pulse, 40 ms), and prepulse trials—in which each tone of 120 dB (also 40 ms) was preceded by a prepulse of 75 dB (duration, 20 ms), and applied 100 ms before acoustic stimuli of 120 dB.

Either of the two acoustic stimuli was applied 20 times to each rat, and was separated by inter-stimulus intervals of 20 sec. Acoustic stimuli in blocks of 20 were applied to each animal in an order arranged according to the latin square. Since the effects of prepulse alone in control and MK-801-treated animals were below a threshold of 10 g, those stimulation parameters were not included in the present experimental protocol (Wędzony et al. 1994). MK-801 (0.4 mg/kg, i.p.) was given 30 min before the experiment, whereas WAY 100135 (1.25, 2.5, 5, 10, and 20 mg/kg, i.p.) was injected 10 min before MK-801.

The startle data were presented as described previously (Wędzony et al. 1994). Briefly, amplitudes of each type of trial were averaged out individually for each animal, and the mean amplitude was calculated for a given group of animals. The following formula was used to calculate a percentage of prepulse-induced inhibition in individual animals: (average amplitude of pulse-alone trials − average amplitude of prepulse, followed by pulse trials/average amplitude of pulse-alone trials) × 100. A high percentage of scores indicates a high degree of prepulse inhibition.

Delayed Alternation Task

The experiment was performed on animals which had been trained to pick-up food pellets alternately from the left and the right arms of a T-maze. Acquisition of behavior of this type consists of three distinct phases: extensive handling, handling and adaptation to the T-maze, and training.

T-Maze. The T-maze consisted of two arms and a central alley with walls. Each part of the maze (68 cm long, 35 cm high, 17 cm wide) was made of wood covered with dark-brown-painted plastic. A small cup with opaque walls was placed at the end of each arm. Noyes precision food pellets, (P.J. Noyes Company Inc., Lancaster, NH) (45 mg) were used as a reinforcement. The experiment was performed in a lighted room with several external cues placed in a fixed configuration.

Handling and Training. The animals were assigned to a trained investigator and were tested five days a week at the same time. They were habituated to a T-maze for one week. During the habituation phase, groups of the rats were allowed to explore the maze freely for 15 min per session; food pellets were randomly available in all the arms of the maze. In the following week, the food pellets were placed at the end of each arm and the rats were put individually into the maze. In the third week, the rats began to be trained in a delayed alternation task.

In the first trial of the delayed alternation, the animals were rewarded for entering either arm of the maze. Thereafter, during a total of 10 trials per session, the rats were rewarded only when they entered an arm which had not been chosen previously. A 10-second delay between successive trials was rigorously controlled, during which the animals were removed from the maze. The training was continued until a criterion of 80% of the correct choices on two consecutive days was fulfilled; it took 10–14 days to meet this criterion. Animals that did not satisfy the above-mentioned criterion within 20 days were discarded. Approximately 10% of the animals belonged to the latter group.

Drug Effects. Tests showing drug effects were carried out once a week, whereas on the remaining four days, the rats were subjected to a training session only. MK-801 (0.2 mg/kg, i.p.) was given 30 min before the test, whereas WAY 100135 (1.25, 2.5, and 5 mg/kg, i.p.) was injected 10 min before MK-801.

Data are given as the number of incorrect choices during a session in which every rat was tested 10 times. An incorrect choice was defined as an entry into a non-baited arm. In addition, we measured the average time needed to complete the task in order to control possible impairment of the locomotion, which might have led to false positive results. Finally, we calculated the maximum number of consecutive entries to the same arm in order to determine whether WAY 100135 was able to reduce the number of perseverative mistakes, typical of MK-801.

In Situ Hybridization Histochemistry

Rats were killed by decapitation 2 and 24 hours after MK-801 (0.4 mg/kg) administration. Their brains were removed and rapidly frozen in dry ice-cold isopentane and stored at −70°C until sectioning. Coronal sections (10 μm) were cut out at a level of the hippocampus using the Leica cryostat LC 3000, and were thaw-mounted onto subbed glass microscope slides. Prior to hybridization, tissue sections were fixed for 10 min at 0°C in a solution of 4% paraformaldehyde-0.01M phosphate-buffered saline (PBS), pH 7.0. The slides were then washed for 10 min in PBS (at a room temperature), and acetylated for 10 min in a mixture of 0.1M triethanolamine (pH 8) and 0.25% acetic anhydrate. After dehydration in graded ethanol, the sections were defatted twice in chloroform for 5 min, rinsed in graded ethanol, and air-dried.

For an *in situ* hybridization assay of 5-HT1A receptor mRNA, the tissue sections were hybridized with a probe containing two 30-mer synthetic oligodeoxynucleotides (GENSET, mixed in the proportion 1:1) complementary to 175–184 and 262–271 amino-acid sequences of rat 5-HT_{1A} receptor (Liao et al. 1993).The probe was labelled using an [α-^{35}S]dATP (NEN) with terminal transferase (Boehringer-Mannheim, Mannheim, Germany). The labelled probe was then purified on a BioRad spin column and showed a final specific activity of ca. 3×10^5 dpm/μl. The sections were hybridized with a [^{35}S]dATP-labelled probe (100 μl/slide), diluted to a final concentration of 2.45×10^5 dpm/ml in a hybridization buffer (50% deionized formamide; 4 × SSC; 25 mM sodium phosphate, pH 7.0; 1mM sodium pyrophosphate; 1× Derhardt's solution; 200 μg/ml salmon sperm DNA; 100 μg/ml polyadenylic acid; 10% dextran sulphate; and 250 μg/ml yeast tRNA) for 20 h at 42°C in a humidified chamber.

After incubation, the sections were rinsed in 1× SSC buffer (at a room temperature), then the slides were washed again three times in 1 × SSC buffer at 55°C for 15 min, and again in 1 × SSC buffer (at a room temperature, for 30min). Finally, the slides were rinsed in 0.1 × SSC buffer and sterile water. After washing, the slides were dehydrated in graded ethanol, dried, exposed to an X-ray film (Hyperfilm-β_{max}; Amersham, Cleveland, OH) for 20 days at −4°C, and then developed in a Kodak D-19 developer. The autoradiograms were analyzed using an image analysis system (SPOT-32 digital camera, Image ProPlus program, Media Cybernetics, Silver Spring, MD).

For quantification, the mean optical density of a specific hybridization signal was measured in various hippocampal regions. Non-specific labelling of the used oligoprobe was determined from an area of sections showing an apparent lack of the hybridization signal. Hippocampal sub-fields were identified with reference to cresyl violet-stained sections and to an anatomical atlas of Paxinos and Watson (1986). In order to further verify the specificity of the labelling—cellular distribution of 5-HT1A specific mRNA—the sections were covered with a photographic emulsion (Kodak NBT3). After 18 weeks, the sections were developed with a Kodak D19 developer and counter-stained with cresyl violet. The distribution of silver grains was inspected using a Nikon Optiphot 2 microscope (Nikon Europe B.V. Badhovevedrop, NL) under high power magnification (40X objective).

Drugs

The following drugs were used: MK-801 maleate (RBI, Natic, MA) and WAY 100135 (IF, PAN, Krakow, PL). Both these drugs were dissolved in physiological saline

and administered in a volume of 2 ml/kg per body weight. All other reagents (molecular grade) for *in situ* hybridization were purchased from Sigma, St. Louis, MO.

Data Presentation and Statistics

A two-way analysis of variance (ANOVA) was used for all the experimental series. The Dunnett (a locomotor activity test, sensorimotor gating, *in situ* hybridization) or the Newman-Keuls (a delayed alternation task) tests were used for *post hoc* comparisons.

RESULTS

Effects of WAY 100135 on MK-801-Induced Locomotor Hyperactivity

MK-801 given in a dose of 0.4 mg/kg induced a long-lasting locomotor hyperactivity which reached a level of significance in comparison with vehicle-treated animals in the first 20 min after injection and lasted over 2 hours (Figure 1). WAY 100135, given alone in doses of 5, 10, and 20 mg/kg did not influence the locomotor activity of rats; however, the doses of 10 and 20 mg/kg, given 10 min before MK-801, attenuated the locomotion- stimulating effects of MK-801 (0.4 mg/kg) (Figure 1). The two latter doses of WAY 100135 evoked a similar maximal effect, however the effect of a dose of 20 mg/kg lasted longer than that of 10 mg/kg. When used in a dose of 5 mg/kg, WAY 100135 was ineffective towards the locomotion-stimulating effect of MK-801. In all the tested doses (5, 10, and 20 mg/kg), WAY 100135 had no effect on the MK-801-evoked stereotyped behavior, assessed automatically (data not shown).

In a separate set of experiments, the effect of WAY 100135 in lower doses (1.25 and 2.5 mg/kg) was tested against MK-801-induced locomotor hyperactivity (0.4 mg/kg). At these low doses, WAY 100135 did not influence either spontaneous locomotion or MK-801 evoked locomotor hyperactivity (data not included).

Effects of WAY 100135 on MK-801- Induced Deficits in Sensorimotor Gating

In our experimental paradigm, we observed that a weak acoustic prepulse lowered the amplitude of the startle reflex to the consecutive tone, which indicates that specific parameters of acoustic stimulation were correctly selected to measure the phenomenon of sensorimotor gating. MK-801 (0.4 mg/kg) attenuated the magnitude of prepulse-induced inhibition of the acoustic startle response (Figure 2B). That magnitude, observed in vehicle- and MK-801-treated animals, was in line with the data reported by other authors (Mansbach and Geyer 1989).

In our experiment, MK-801 did not influence the amplitude of the acoustic startle response (Figure 2A). WAY 100135, given alone in doses of 1.25–20 mg/kg,

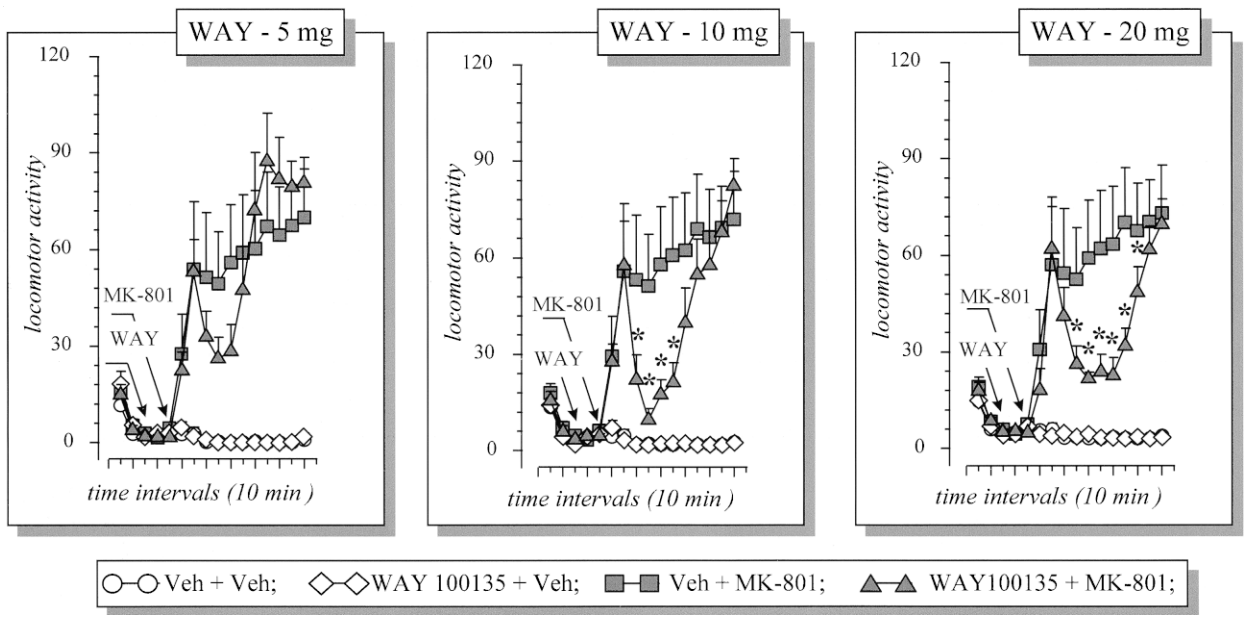

Figure 1. The influence of various doses of WAY 100135 on the MK-801-induced locomotor hyperactivity in rats. WAY 100135 was given in doses of 5, 10, and 20 mg/kg after habituation to Optovarimex cages which lasted 30 min, and 10 min before administration of MK-801 (0.4 mg/kg). The time of administration of the respective drugs is indicated by arrows. Each data point represents an average locomotor activity per group ± SEM. For the sake of clarity, only differences between MK-801- and WAY 100135- plus MK-801-treated animals are indicated with asterisks. For a statistical analysis, a two-way ANOVA (time versus drug treatment), followed by the Dunnett test were used; $^*p < .05$, $n = 10$ for each group.

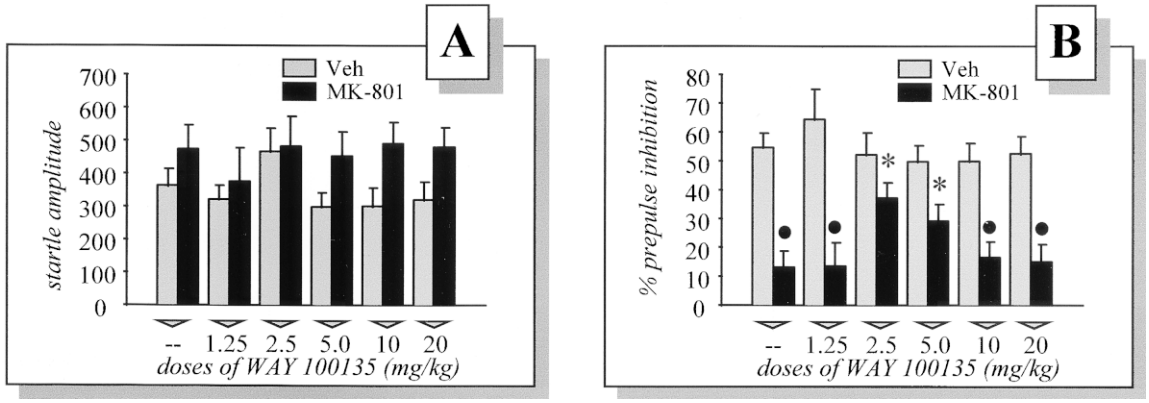

Figure 2. The influence of WAY 100135 on the MK-801-evoked deficits in prepulse induced inhibition of the acoustic startle response. **(A)** Impact of various doses WAY 100135 (1.25, 2.5, 5, 10, and 20 mg/kg), MK-801 (0.4 mg/kg) and their combination on the amplitude of the acoustic startle. **(B)** Impact of various does of WAY 100135 (1.25, 2.5, 5, 10, and 20 mg/kg), MK-801 (0.4 mg/kg) and their combination on the prepulse3-induced inhibition of the acoustic startle response. In **(A)**, bars represent an average amplitude of the startle reflex ± SEM, whereas in **(B)**, they show an average percentage of inhibition ± SEM. Asterisks indicate a statistically significant effect of WAY 100135 on the disruption induced by MK-801 (0.4 mg/kg), whereas filled dots show significant effects of MK-801 in comparison with vehicle-treated animals. A two-way ANOVA was followed by the Dunnett test; $p < .05$, $n = 12$ for each group.

influenced neither the prepulse inhibition (Figure 2B) nor the amplitude of startle reaction (Figure 2A). However, when given 10 min before MK-801 (0.4 mg/kg), WAY 100135 (2.5 and 5 mg/kg) attenuated/blocked the effect of MK-801 on the prepulse-induced inhibition of acoustic startle response (Figure 2B). In doses of 1.25, 10, and 20 mg/kg WAY 100135 was ineffective towards the above effect of MK-801 (Figure 2B). Joint administration of MK-801 (0.4 mg/kg) and WAY 100135 (1.25–20 mg/kg) did not affect the amplitude of the acoustic startle response (Figure 2A).

Impact of WAY 100135 on Detrimental Effects of MK-801 on Working Memory and Selective Attention

MK-801 given in a dose of 0.2 mg/kg disrupted rats' performance in a delayed alternation task, which points to impairment of working memory and selective attention (Figure 3). This effect was reflected in two parameters characteristic of the behavior of rats: the number of errors (Figure 3A) and the number of consecutive entries into the same arm of the T-maze (Figure 3B). At the same time, MK-801 (0.2 mg/kg) did not influence the average time required to complete the task, which suggests that the apparent increase in the number of errors did not result from impairment of the locomotion (Figure 3C).

WAY 100135 in doses of 1.25, 2.5, and 5 mg/kg did not alter the performance of rats in the delayed alternation task, which was reflected in a lack of changes in all the three parameters (Figures 3A, B, and C). Although WAY 100135 was ineffective when given alone, it attenuated (in the dose of 2.5 mg/kg) the deficits in working memory and selective attention evoked by MK-801 (0.2 mg/kg) (Figures 3A and B). The latter dose of WAY 100135 reduced the number of errors (Figure 3A), and attenuated the perseverative type of behavior reflected in the decreased number of consecutive entries into the same arm of the T-maze (Figure 3B). In a dose of 1.25 mg/kg, WAY 100135 reduced the number of the consecutive entries only (Figure 3B). Joint administration of WAY 100135 and MK-801 did not influence the time required to complete the behavioral task (Figure 3C).

Impact of MK-801 on mRNA Encoding 5-HT1A Receptors in Rat Hippocampus

We observed a distinct labelling of the 5-HT1A receptor mRNA in all major regions of the hippocampus (Figure 4A). The labelling has been mainly associated with cell bodies (Figure 4B). The highest density of mRNA was found in the dentate gyrus, and the lowest in dorsal parts of the CA1 region (Figure 5). That apparent distribution of mRNA of the 5-HT1A receptors was in line with some earlier findings of Liao et al. (1993). We found that MK-801 in a dose of 0.4 mg/kg did not influence the amount of 5-HT1A receptor mRNA, measured 2 and 24 hours after MK-801 injection (Figure 5).

DISCUSSION

Locomotor Activity

WAY 100135 attenuated the locomotor hyperactivity induced by MK-801 in rats. This effect confirms earlier findings of Loscher and Honack (1992, 1993), and

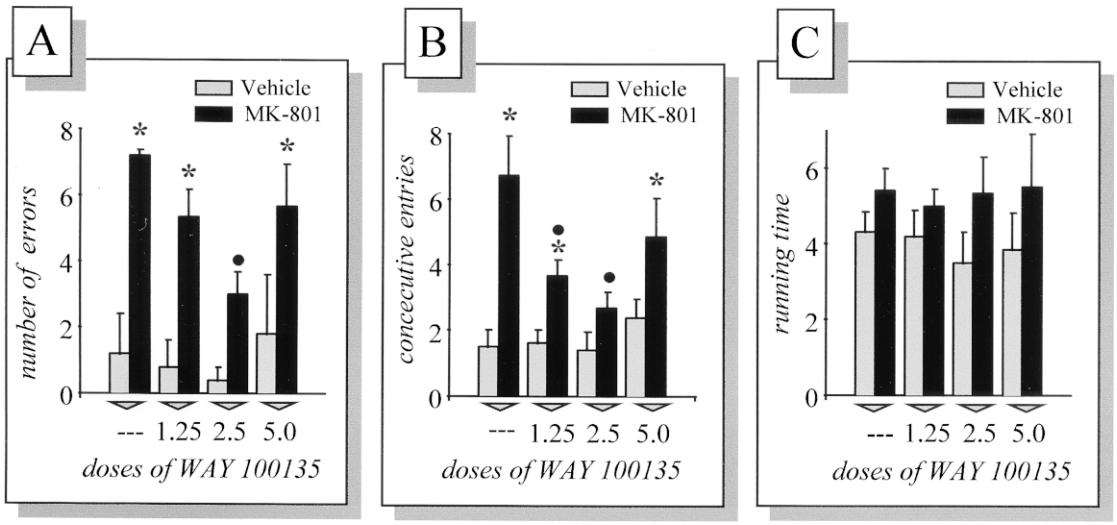

Figure 3. The effect of WAY 100135 on the detrimental effects of MK-801 on spatial working memory and selective attention of rats, measured in a delayed alternation task. WAY 100135 (1.25, 2.5, and 5 mg/kg, i.p.) was given 10 min before the test, whereas MK-801 (0.4 mg/kg) 30 min before. The rats' performance in the delayed alteration task is shown by three parameters: **(A)** the number of errors; **(B)** consecutive entries to the same arm of the T-maze; and **(C)** the running time (sec). The data are given as mean ± S.E.M. of 10 trials; $n = 6–8$; asterisks indicate statistically significant differences in comparison with vehicle-treated animals; a two-way ANOVA was followed by the Newman-Keuls test.

strengthens the suggestion that drugs operating via the 5-HT1A receptor are able to influence the psychostimulant effects of non-competitive NMDA receptor antagonists (Loscher and Honack 1992, 1993). The effect of WAY 100135, although potent, was transient. This transient effect is difficult to explain since in brain microdialysis experiments, WAY 100135 produced a long-lasting effect on the 8-OHDPAT and ipsapirone-evoked alterations in serotonin and dopamine release (Assie and Koek 1996; Wędzony et al. 1996b).

Considering the fact that the effective doses of WAY 100135 used in this model were relatively high (Assie and Koek 1996), it cannot be ruled out that the observed effect of WAY 100135 on the MK-801-evoked locomotor hyperactivity was due to its transient partial agonistic properties, found in some experimental models (Assie

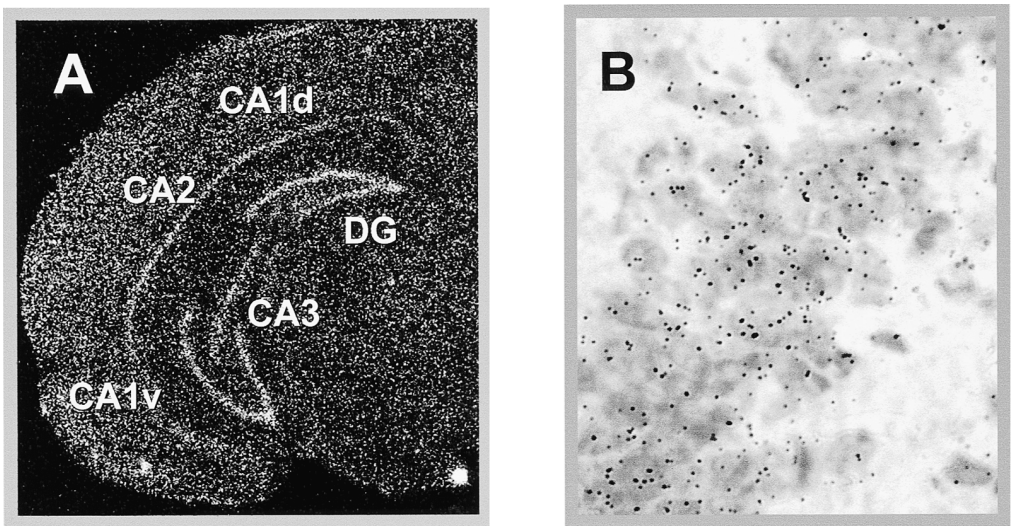

Figure 4. Representative distribution of the 5-HT1A serotonin receptor mRNA at a level of rat hippocampus. **(A)** A film autoradiography. **(B)** Bright-field photomicrography (objective 40X) of the dorsal CA1 region of the hippocampus showing silver grains corresponding to the 5-HT1A receptor mRNA that overlay cell bodies, possibly of hippocampal pyramidal neurons counterstained with cresyl violet.

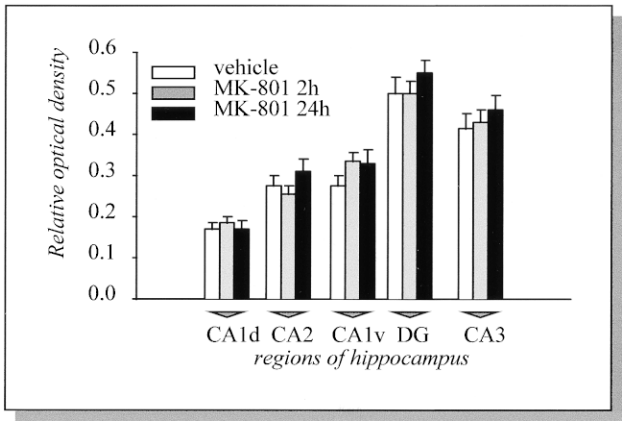

Figure 5. The impact of MK-801 on the expression of mRNA of 5-HT1A receptors in rat hippocampus. MK-801 (0.4 mg/kg) was given 2 and 24 hours before decapitation. The 5-HT1A receptor mRNA level is shown as a relative optical density measured in different sub-regions of the hippocampus, and obtained from at least five animals (mean ± SEM). *Abbreviations:* CA1 d, dorsal CA1 region; CA1 v, ventral CA1 region; DG, dentate gyrus.

and Koek 1996). In favor of this concept are studies showing that agonists of 5-HT1A receptors attenuate not only the locomotor stimulant effects of amphetamine and MK-801 (Loscher and Honack 1992; Przegalinski and Filip 1997), but also the amphetamine-evoked enhancement of dopamine release (Kuroki et al. 1996; Ichikawa et al. 1995). Arguments that drugs operating via 5-HT1A receptors evoke alterations in dopaminergic neurotransmission, are relevant, since several studies have indicated that MK-801-induced hyperactivity is associated with enhancement of dopaminergic neurotransmission (Maj et al. 1991; Adams and Moghaddam 1998; Wędzony et al. 1993; Svensson et al. 1991). Thus, the most probable explanation of the apparent antagonism of the MK-801-induced locomotor hyperactivity is that WAY 100135 blocks the MK-801-evoked dopamine release. The above explanation is supported by data indicating that agonists and antagonists of 5-HT1A receptors alter dopaminergic neurotransmission (Rasmusson et al. 1994; Wędzony et al. 1996b; Arborelius et al. 1993; Gobert et al. 1998).

It is noteworthy that some experiments failed to observe an interaction between MK-801 and WAY 100135 at a level of locomotor activity (Maj et al. 1996). This discrepancy may result from two facts. First, the effect of WAY 100135, however strong, is transient and may be obscured by the potent long-lasting stimulatory effect of MK-801, especially when results are presented in a cumulative manner (Maj et al. 1996). Secondly, in the present study we used an experimental procedure which differentiated between locomotion and stereotyped behavior concomitant with locomotor hyperactivity, the latter being unaffected by WAY 100135.

Prepulse-Induced Inhibition of Acoustic Startle Response

We found that WAY 100135 attenuated deficits in sensorimotor gating induced by MK-801 (Mansbach and Geyer 1989; Wędzony et al. 1994). This finding suggests that the MK-801-induced impairment of sensorimotor gating is linked, at least partly, with serotonergic neurotransmission engaging 5-HT1A receptors (Loscher and Honack 1993; Wędzony et al. 1997). Furthermore, these studies indicate that drugs operating via 5-HT1A receptors (e.g., WAY 100135) may be of considerable value as potential therapeutic agents to ameliorate cognitive disturbances modeled by this experimental paradigm.

The involvement of 5-HT1A receptors in the regulation of sensorimotor gating has been demonstrated previously. Specifically, 8-OHDPAT (Sipes and Geyer 1995), buspirone, gepirone, and ipsapirone (Rigdon and Weatherspoon 1992), similar to hallucinogens (Geyer 1998; Sipes and Geyer 1994), non-competitive antagonists of NMDA receptors (Mansbach and Geyer 1989; Wędzony et al. 1994; Bakshi and Geyer 1998), and psychostimulants (Swerdlow et al. 1990) abolish PPI. It was also shown that the detrimental effect of 8-OHDPAT on the process of sensorimotor gating was antagonized by WAY 100135 (Sipes and Geyer 1995), which confirms an involvement of 5-HT1A receptors .

Interestingly, studies using intracerebral drug administration technique showed that alterations of PPI by 5-H1A receptor agonists are mediated by somatodendritic receptors on cell bodies of serotonergic neurons within the raphe nucleus (Sipes and Geyer 1995). Although all these effects suggest the neuronal circuit that is probably engaged in propagation of the effects initiated by blockade of NMDA receptors, and brain structures involved in the beneficial action of WAY 100135 on the disruptive effects evoked by MK-801, they do not allow for simple association of the above psychotomimetic effects of MK-801 with the enhancement of serotonin release and turnover (Whitton et al. 1992) after similar doses of MK-801 (Loscher et al. 1991; Wędzony et al. 1997) since, activation of somatodendritic 5-HT1A receptors decreases the release of serotonin from terminals (Sharp et al. 1989). One possible explanation of this discrepancy is that the activation of 5-HT1A receptors due to an excessive release of serotonin after administration of MK-801 may activate neurons of the locus coeruleus (Hajos-Korcsok and Sharp 1999; Hamamura et al. 1997; Piercey et al. 1994), and subsequently enhance noradrenaline release (Hajos-Korcsok and Sharp 1996). Although it would be worthwhile to verify this neuronal circuit, it seems of interest that the detrimental effect of MK-801, injected to the

hippocampus or amygdala (Bakshi and Geyer 1998, 1999), on sensorimotor gating is also antagonized by prazosin, an alpha-1 receptor antagonist. Thus, neurons controlled by 5-HT1A receptors may constitute an interesting element of the neuronal circuits of noradrenaline-regulated alterations in sensorimotor gating, impaired by non-competitive NMDA receptor antagonists (Bakshi and Geyer 1998, 1999). It is also noteworthy that MK-801 and PCP enhance noradrenaline turnover (Yan et al. 1997; Loscher and Honack 1992). It would be of interest to find out whether the above phenomenon involves 5-HT1A receptors. Irrespective of the above speculations, it must be stressed that WAY 100135 is effective at a narrow range of doses only. However, the same doses are sufficient to antagonize the detrimental effects of 8-OHDPAT (1.25 mg/kg) on PPI (Czyrak et al., manuscript in preparation). The cause of the dose-response relationship resembling an inverted U-shape curve is unknown.

In the regulation of MK-801-induced disruption of PPI in rats, it is not clear whether the role of 5-HT1A receptors will apply to all species. Since it has been demonstrated in mice that 8-OHDPAT does not influence the process of sensorimotor gating in a fashion similar to that observed on rats (Dulawa et al. 1997). Rat strain differences observed in PPI paradigm should be also taken into account in this respect (Swerdlow et al. 1998; Kinney et al. 1999).

Spatial Working Memory and Selective Attention

Beneficial effects of WAY 100135 on the MK-801-evoked psychotomimetic effects were also observed in a delayed alteration task, an experiential procedure measuring the efficacy of working memory (Verma and Moghaddam 1996; Romanides et al. 1999). WAY 100135 reduced the number of errors and the maximal number of consecutive entries induced by MK-801, which indicates that it had a beneficial effect on the cognitive disturbances evoked by MK-801 and again, suggests involvement of 5-HT1A receptors in the psychotomimetic effects of non-competitive NMDA antagonists. The apparent impact of WAY 100135 on the detrimental effects of MK-801 on working memory is not surprising, since several reports indicate that drugs acting as antagonists of 5-HT1A receptors, are capable of reversing the deficits of working memory and spatial learning, evoked by agonists of 5-HT1A receptors (Ohno et al. 1993), scopolamine (Ohno and Watanabe 1996; Carli et al. 1995), NMDA receptor antagonists (Carli et al. 1997, 1999), and even by a transection of the fornix (Harder et al. 1996). It is postulated that stimulation of hippocampal 5-HT1A receptors or blockade of hippocampal muscarinic or NMDA receptors, decreases the excitability of hippocampal pyramidal neurons, indispensable for the proper functioning of spatial learning and working memory (Carli et al. 1995). Blockade of 5-HT1A receptors may abolish the above effect and restore the appropriate level of excitation through an attenuation of inhibitory effects of serotonin on hippocampal output neurons (Carli et al. 1995).

All given arguments seem to suggest that the disruptive effects of MK-801 on working memory originate from: 1) blockade of hippocampal NMDA receptors located on the pyramidal neurons (Wędzony and Czyrak 1997); and/or 2) an excessive release of serotonin, which was earlier demonstrated (Whitton et al. 1992; Loscher et al. 1991; Wędzony et al. 1997). However, a question arises whether the hippocampus is the only structure (or element) of a neuronal circuit involved in the detrimental effects of MK-801 on working memory, and in beneficial effects of 5-HT1A receptor antagonists.

An alternative neuronal circuit may involve the prefrontal cortex (Arnsten 1997; Goldman-Rakic 1996). It was shown previously that levels of dopamine that are below or above the physiological optimum promote poor efficacy of working memory (Arnsten 1997). It is known that MK-801 and other non-competitive antagonists of NMDA receptors enhance release of dopamine in the prefrontal cortex, which may disrupt working memory (Moghaddam et al. 1997; Wędzony et al. 1993).

The involvement of dopamine in the detrimental effects of antagonists of glutamatergic receptors (Romanides et al. 1999) on working memory is further supported by observations that their effects are antagonized by dopamine receptor antagonists (Verma and Moghaddam 1996; Romanides et al. 1999). However, a question arises whether blockade of serotonergic receptors of the 5-HT1A subtype would normalize the impairment of dopaminergic neurotransmission, potentially responsible for impairments of working memory. Several arguments are in favor of such a possibility. Selective agonists of 5-HT1A receptors have been shown to preferentially enhance the release of dopamine in the prefrontal cortex (Gobert et al. 1998; Rasmusson et al. 1994; Wędzony et al. 1996b), and enhance the bursting activity of dopaminergic neurons innervating the prefrontal cortex (Arborelius et al. 1993; Pessia et al. 1994; Lejeune and Millan 1998). Some of these effects of 5-HT1A agonists are blocked by WAY 100135 or WAY 100635, antagonists of 5-HT1A receptors (Wędzony et al. 1996b; Lejeune and Millan 1998; Gobert et al. 1998), which points to a functional role of 5-HT1A receptors in the regulation of a subset of dopaminergic neurons innervating the prefrontal cortex and regulating the efficacy of working memory (Romanides et al. 1999). These two alternative neuronal circuits involving the hippocampus and the prefrontal cortex are not exclusive; hence, it is also conceivable that hippocampal 5-HT1A receptors may indirectly influence the activity of glutamatergic neurons innervating the prefrontal cortex, and, as has been shown recently for thalamocortical pathways (Romanides et al.

1999), may also control the efficacy of working memory (Seamans et al. 1998; Floresco et al. 1997).

It is also noteworthy that WAY 100635, an antagonist of 5-HT1A receptors devoid of partial agonistic properties (Gobert et al. 1998), reversed the impairment of working memory and spatial learning (Boast et al. 1999; Carli et al. 1997, 1999), which indirectly suggests that the effects of WAY 100135, observed in our study, are due to the blockade of 5-HT1A receptors.

The 5-HT1A Receptor mRNA

We observed that a single administration of MK-801 did not alter the amount of mRNA encoding 5-HT1A receptor synthesis in rat hippocampus. This observation is interesting since our earlier findings showed that MK-801, given in the same dose and according to the same time regime, increased the number of 5-HT1A receptor binding sites (Wędzony et al. 1997). The lack of correlation between the level of mRNA and changes in the receptor binding may indicate that the receptor alterations described previously (Wędzony et al. 1997) are not due to the effect of MK-801 on the efficacy of 5-HT1A receptor transcription. Interestingly schizophrenic patients display an elevated level of 5-HT1A receptor bindings sites, without any significant changes in 5-HT1A receptor mRNA (Burnet et al. 1996; Simpson et al. 1996). Thus, in MK-801-treated animals the profile of changes in 5-HT1A receptors, is very similar to those seen in schizophrenic patients (Burnet et al. 1996).

GENERAL CONCLUSIONS

Summing up, our present study indicates that WAY 100135, a substance operating via 5-HT1A receptors, attenuates the psychostimulant and psychotomimetic effects of non-competitive antagonists of NMDA receptors. Interestingly, the effective doses of WAY 100135 differ in the models employed. These differences may stem from different neuronal circuits engaged, involvement of somatodendritic or postsynaptic 5-HT1A receptors and from diverse 5-HT1A receptor reserves (Meller et al. 1990) in various regions of the brain. It is speculated that the locomotor hyperactivity evoked by MK-801 is blocked as a result of a partial agonistic activity, while cognitive disturbances seem to be improved due to antagonistic effects of WAY 100135 at 5-HT1A receptors.

Our present study also indicates that serotonin receptors of the 5-HT1A type are engaged in the psychotomimetic effects of MK-801 suggesting that in the future it may be of interest to search for novel neuroleptic drugs which exert their antipsychotic effects via 5-HT1A receptors. This future research could focus not only on drugs with partial agonistic activity at 5-HT1A receptors (which has recently been discovered for clozapine and ziprasidone (Rollema et al. 1997; Sprouse et al. 1999), but also on full antagonists. The above findings are of considerable interest, since in schizophrenic patients an increase in the level of 5-HT1A receptors in the cerebral cortex and hippocampus has been demonstrated (Burnet et al. 1996; Simpson et al. 1996) suggesting again that 5-HT1A receptors should be considered as a novel potential target in the treatment of certain cognitive disturbances of schizophrenia.

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