1996_padich_1

ORIGINAL INVESTIGATION

Robert A. Padich · Timothy C. McCloskey
John H. Kehne

5-HT modulation of auditory and visual sensorimotor gating: II. Effects of the 5-HT_{2A} antagonist MDL 100,907 on disruption of sound and light prepulse inhibition produced by 5-HT agonists in Wistar rats

Received: 16 March 1995 / Final version: 18 October 1995

Abstract Increasing evidence suggests an important role of 5-HT, and 5-HT_{2A} receptors in particular, in the etiology and treatment of schizophrenia. The prepulse inhibition paradigm is used as a model for sensorimotor gating processes that are disrupted in schizophrenia. The present study used the selective serotonin$_{2A}$ (5-HT_{2A}) antagonist and putative antipsychotic agent MDL 100,907 to evaluate the contribution of 5-HT_{2A} receptors to the disruptions of prepulse inhibition produced by several 5-HT agonists. The D_2 antagonist haloperidol was used to evaluate a possible interaction with dopamine neurons. Sound or light prepulses were used to measure the generality of these drug effects on cross-modal prepulse inhibition. In the first study, MDL 100,907 antagonized the disruptions of auditory prepulse inhibition produced by the 5-HT releasing agents fenfluramine and 3,4-methylenedioxymethamphetamine (MDMA). These effects on prepulse inhibition were modality-specific in that MDL 100,907 did not reverse the effects of the 5-HT releasers on visual prepulse inhibition. Haloperidol did not alter the disruptive effects of MDMA or fenfluramine on either auditory or visual prepulse inhibition. In the second study, the direct acting 5-$HT_{2A/2C}$ receptor agonist/hallucinogen (+)1-4-iodo-2,5-dimethoxyphenyl-2-aminopropane (DOI) consistently disrupted auditory prepulse inhibition, and this effect was blocked by MDL 100,907 but not by haloperidol. A dose-response analysis demonstrated that MDL 100,907 potently antagonized DOI disrupted auditory prepulse inhibition, with an ED_{50} of 0.04 mg/kg, IP. DOI did not consistently disrupt visual prepulse inhibition. In summary, these data indicate that, at least under the conditions of the present studies, the disruptions of auditory prepulse inhibition produced by fenfluramine, MDMA, and DOI result from stimulation of 5-HT_{2A} receptors. Furthermore, these disruptions do not involve direct or indirect stimulation of D_2 receptors. The identity of the 5-HT receptor(s) underlying the disruptive effects of fenfluramine or MDMA on visual prepulse inhibition has not yet been identified. MDL 100,907 may be generally useful in CNS disorders in which excessive 5-HT_{2A} receptor tone disrupts sensory gating processes.

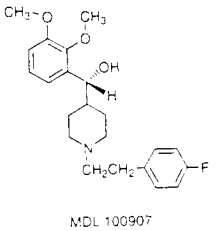
Key words Prepulse inhibition · Sensorimotor gating · Schizophrenia · Wistar rats · Serotonin · 5-HT_{2A} receptor · MDL 100,907 · 3,4-Methylenedioxymethamphetamine, MDMA · Fenfluramine · (+)1-4-Iodo-2,5-dimethoxyphenyl-2-aminopropane, DOI

R.A. Padich · T. C. McCloskey · J. H. Kehne(✉)
Hoechst Marion Roussel Inc., 2110 E. Galbraith Road, Cincinnati, OH 45215, USA

Introduction

The dopamine (DA) hypothesis of schizophrenia has traditionally emphasized the critical role of dopaminergic neurons in the etiology and treatment of schizophrenia. However, increasing evidence suggests an important contribution of 5-HT (see Breier 1995, for a recent review). The contribution of 5-HT_{2A} receptors has gained particular attention (Meltzer et al. 1989; Meltzer 1991; Leysen et al. 1993; Schmidt et al. 1993, 1995). For example, many hallucinogenic agents which disrupt sensorimotor gating processes are noted for their actions on serotonergic pathways, and some antipsychotic agents, including the atypical antipsychotic clozapine and the new antipsychotic risperidone, have potent antagonist actions at 5-HT_{2A} receptors which may contribute to their antipsychotic profile.

Until recently, study of the involvement of 5-HT_{2A} receptors in schizophrenia has been hampered by the lack of a highly selective 5-HT_{2A} antagonist. MDL 100,907 (see Fig. 1 for structure) has subnanomolar potency in 5-HT_{2A} receptor binding assays in vitro (Palfreyman et al. 1993; Kehne et al. 1996a; Schmidt et al. 1995) and shows at least a 100-fold separation from 26 other receptors, including the 5-HT_{2C}, α_1-adrenergic, σ, D_1, D_2, D_3, and D_4 dopamine receptors (Palfreyman et al. 1993; Kehne et al. 1996a). Functional studies in vitro demonstrated that MDL 100,907 has subnanomolar potency in



MDL 100907

Fig. 1 The chemical structure of MDL 100,907

blocking 5-HT stimulated inositol phosphate accumulation in cells transfected with the 5-HT_{2A} receptor and is over 1000-fold less potent in blocking 5-HT_{2C} mediated responses (Kehne et al. 1996a). Functional studies in vivo show potent activity in a 5-HT_{2A} headtwitch assay in mice (ED_{50}=0.03 mg/kg, IP), and a greater than 500-fold separation from in vivo activities indicative of D_2 dopamine or α_1-adrenergic receptor antagonism (Kehne et al. 1996a). Electrophysiological studies in piriform cortex interneurons have demonstrated that MDL 100,907 is a potent and reversible 5-HT_{2A} antagonist, in contrast to mixed 5-$HT_{2A/2C}$ antagonists such as ritanserin (Marek and Aghajanian 1994). These and other data indicate that MDL 100,907 is a useful pharmacological tool for evaluating the role of 5-HT_{2A} receptors (Schmidt et al. 1995).

In vivo studies have demonstrated that MDL 100,907 is active in a number of antipsychotic models (Sorensen et al. 1993; Kehne et al. 1996a; Moser et al. 1996; Schmidt et al. 1995). For example, MDL 100,907 administered chronically (1 mg/kg, 21 days) selectively reduces the number of spontaneously active DA neurons in the A10 (but not A9) nucleus in rats, a profile seen with the atypical antipsychotic clozapine (Sorensen et al. 1993). Furthermore, MDL 100,907 reduces *d*-amphetamine stimulated locomotion in mice (ED_{50} in mice=0.08 mg/kg) (Kehne et al. 1996a) and 1.0 mg/kg reversed *d*-amphetamine disrupted latent inhibition in rats (Moser et al. 1996). Based upon these and other studies, MDL 100,907 is being developed as an antipsychotic agent (Schmidt et al. 1995, Kehne et al. 1996a).

Prepulse inhibition is being increasingly used as a model of sensorimotor gating for studying the neurobiology of schizophrenia (Braff and Geyer 1989; Geyer et al. 1990; Swerdlow et al. 1990) and for identifying and characterizing novel antipsychotic agents (Rigdon and Viik 1991; Swerdlow et al. 1991). In this model, a weak stimulus such as an auditory stimulus (sound) or a visual stimulus (light) presented at a short interval (e.g. ≤100 ms) before a strong, startle-response-eliciting stimulus, reduces the normal response to the strong stimulus. This reduction in response amplitude by the weak prestimulus is operationally defined as prepulse inhibition. Prepulse inhibition using an eyeblink component of the startle response is disrupted in schizophrenics (Braff and Geyer 1989; Geyer et al. 1990; Grillon et al. 1992; Judd et al. 1992; Karper et al. 1993). Furthermore, drugs which produce psychotic-like symptoms in humans can disrupt prepulse inhibition in humans and in animals (Mansbach et al. 1988; Swerdlow et al. 1990, 1991; Mansbach 1991; Sipes and Geyer 1994).

Given the suggested importance of 5-HT_{2A} receptors to the neurobiology of schizophrenia and to the mechanism of antipsychotic agents, it would be desirable to investigate the role of 5-HT_{2A} receptors in sensorimotor gating processes as measured with prepulse inhibition. Previous work demonstrated that four agents which shared the common property of being 5-HT releasers, i.e. *p*-chloroamphetamine (PCA); 3,4-methylenedixoymethamphetamine (MDMA); *N*-ethyl-3,4-methylenedixoymethamphetamine (MDEA); or fenfluramine (Schmidt and Kehne 1990; Schmidt and Taylor 1990; Berger et al. 1992) disrupted auditory (Mansbach et al. 1989; Kehne et al. 1996b) and visual (Kehne et al. 1996b) prepulse inhibition in rats. The disruptive effects of fenfluramine on both auditory and visual prepulse inhibition could be attenuated by either a 5-HT uptake blocker (which prevented carrier-mediated 5-HT release) or by a 5-HT neurotoxin (which lesioned 5-HT terminals), suggesting that the effects of this agent were mediated by 5-HT neurons.

Though general 5-HT involvement was demonstrated, the specific 5-HT receptors mediating the disruptive effects of fenfluramine on auditory and visual prepulse inhibition were not investigated. Currently, numerous 5-HT receptor subtypes have been identified, including 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_4, 5-HT_5, 5-HT_6, and 5-HT_7 (for review, see Peroutka 1994). Several studies have shown that agonists for the 5-HT_{1A} receptor (Rigdon and Weatherspoon 1992; Sipes and Geyer 1995) or the 5-HT_{1B} receptor (Sipes and Geyer 1994) disrupt auditory prepulse inhibition.

Another possible candidate is the 5-HT_{2A} receptor. (+)1-4-Iodo-2,5-dimethoxyphenyl-2-aminopropane (DOI), a hallucinogen which is known to stimulate 5-$HT_{2A/2C}$ receptors (Glennon 1986; Titeler et al. 1987; Appel et al. 1990; Pranzatelli 1990), disrupted auditory prepulse inhibition in rats and this effect was reversed by the 5-HT_{2A}/α_1-adrenergic antagonist ketanserin (Sipes and Geyer 1994). The 5-HT_{2C} agonist [1-(*m*)-chlorophenyl-piperazine] (mCPP) did not disrupt prepulse inhibition, supporting the importance of 5-HT_{2A} versus 5-HT_{2C} receptors in the DOI-induced disruption of prepulse inhibition (Sipes and Geyer 1994).

The primary goal of the present study was to use MDL 100,907 to evaluate the contribution of 5-HT_{2A} receptors to disruptions of prepulse inhibition produced by fenfluramine or MDMA, and to confirm the contribution of 5-HT_{2A} receptors to the disruptive effects of DOI on auditory prepulse inhibition. A secondary goal was to use haloperidol to evaluate possible contributions of D_2 receptors to the disruptions of prepulse inhibition produced by MDMA, fenfluramine, and DOI. The rationale for this experiment is upon several lines of anatomical, biochemical, electrophysiological, and behavioral evidence suggesting the presence of 5-HT_{2A}/DA interactions in the CNS (for review, see Schmidt et al. 1995). For example, MDL 100,907 can attenuate the effects of the DA-releasing agent *d*-amphetamine on dopaminergic

firing or on locomotor activity. Recent work has demonstrated that haloperidol can antagonize the effects of DOI on auditory prepulse inhibition (Sipes and Geyer 1994), supporting the possibility of a 5-HT_{2A}/D_2 interaction in the modulation of sensorimotor gating.

Evaluations of prepulse inhibition are typically made using an auditory stimulus as a prepulse. We have initiated exploratory work in which we additionally evaluate drug effects on prepulse inhibition produced by a visual stimulus (Kehne et al. 1996b). Given that little information is currently available on the comparative pharmacology of auditory and visual prepulse inhibition, such analysis may ultimately lead to a better understanding of the neurobiology of sensory gating processes in the brain. As described previously (Kehne et al. 1996b), cross-modal prepulse inhibition was assessed using an auditory stimulus (weak noise-burst) or a visual stimulus (light flash), with both types of prepulses presented within a single test session. Using this approach, the present studies also sought to characterize the effects of DOI on visual prepulse inhibition, as no previous studies have addressed this question.

As in the companion study (Kehne et al. 1996b), Wistar rats were chosen for use in all studies. Our experience is that this strain demonstrates robust levels of startle amplitude relative to other strains, as suggested by Rigdon and Viik (1991), and provides reliable and consistent prepulse inhibition in controls (J.H. Kehne, R.A. Padich, and T.C. McCloskey, unpublished observations).

Materials and methods

Animals

Subjects were experimentally naive, male albino Wistar rats which were housed in groups of four in a colony room maintained on a 14:10 h light/dark cycle (lights on at 6:00 a.m.). Food and water were available ad libitum. Rats were acclimated for at least 1 week from the date of receipt before beginning the experiments.

Prepulse inhibition testing

Apparatus

An apparatus consisting of eight separate stabilimeters measured the amplitude of startle reflexes elicited by acoustic stimulation (see Kehne et al. 1992, for a detailed description). Movement of the platform against a transducer produced a voltage proportional to displacement and was reported in units from 0 to 4095. Each stabilimeter was housed in a ventilated, sound-attenuating chamber illuminated by dim, red-filtered light.

Stimulus parameters

The startle-eliciting stimulus was a 40-ms burst of white noise at a sound pressure level of 120 dBA. The auditory prepulse stimulus was a 20-ms, 78-dB burst of white noise presented 100 ms prior to the eliciting stimulus against a constant 64-dB background of white noise. These parameters were selected to be similar to those used in the majority of the studies reviewed by Geyer et al. (1990).

As mentioned in the Introduction, cross-modal prepulse inhibition by a light stimulus was included to determine if the reported prepulse effects were limited to a single (auditory) modality or more generalized across two modalities. The visual prepulse was created by turning on three incandescent bulbs in the animal chamber (one mounted on the ceiling and one mounted at each end of the test chamber) 75 ms prior to the onset of the startle stimulus. The visual stimulus was turned off 75 ms later. This visual stimulus produced no perceptible or electronically-measurable sound, even when the 65 dB white masking noise was turned off. The estimated rise time of the light prepulse to a peak of about 175 lux was approximately 25 ms. The resultant interval between peak intensity and startle stimulus corresponds to the 50-ms interstimulus interval reported in the literature to be optimal for visual prepulses (Hoffman and Ison 1980). The dim, red background illumination in the chambers averaged <2 lux.

Standard test procedure

After an appropriate pretreatment time, rats were placed in the startle chamber for a 5-min acclimation period. The rats were then presented with three pre-test trials: the first was the startle stimulus alone (no prepulse), followed 20 s later by a sound prepulse alone (no startle stimulus), and then 20 s later by a light prepulse alone (no startle stimulus). The purpose of these pre-test trials was first, to reduce the variability typically seen on the presentation of the first startle stimulus, and second, to demonstrate that the sound or light prepulses do not by themselves produce a startle response. This was followed by 10 min of prepulse inhibition testing: ten trials with a startle stimulus alone (no prepulse), ten trials with a startle stimulus preceded by a sound prepulse, and ten trials with a startle stimulus preceded by a light prepulse. These trials were presented in a pseudorandom order. The intertrial interval of 20 s resulted in a session length of about 16 min, including the 5-min acclimation period. Prepulse inhibition was operationally defined as a rat's decrease in startle amplitude for the startle stimulus + prepulse trial, relative to the startle stimulus alone trial. Prepulse inhibition was quantified as an absolute change score [(startle stimulus alone) – (startle stimulus + prepulse)].

Experimental design

In all experiments, independent groups of rats were used to test different pharmacological agents, or different doses of a given agent. Thus, "Treatment" was a between-subjects variable. All rats were tested only once. Within a given test session, individual scores were generated for each rat for each of three trial types: (1) acoustic startle stimulus preceded by no prepulse ("No Prepulse" condition; NP), which gives a measure of the baseline reactivity of the rat; (2) acoustic startle stimulus preceded by a sound prepulse ("Sound Prepulse" condition; SP) to produce auditory prepulse inhibition; (3) acoustic startle stimulus preceded by a light prepulse ("Light Prepulse" condition; LP) to produce visual prepulse inhibition. Thus, "Trial Type" was a within-subjects variable. Because there were eight individual startle test cages, two independent samples of eight rats each were used for each treatment condition to give a total n=16 per group (unless otherwise noted). For simplicity, within a given test session, all eight rats received the same treatment (i.e. vehicle or specific dose of drug). The second group of eight rats was tested at a different time of day. All testing was carried out during a 6-h window of the light cycle. Our experience has indicated that this test design results in stable, reproducible prepulse inhibition in control and drug-treated rats.

Statistical analyses

For each rat, several scores were derived from the data. "Raw scores", defined as the session means of the ten trials of each trial type (NP, SP, and LP, as described above) were calculated. "Change Scores" were calculated as the difference between baseline (NP) session mean for a rat and either of the two prepulse condition

means (i.e. NP–SP; NP–LP). "Percent Change Scores" were calculated as the difference between baseline (NP) session mean for a rat and either of the two prepulse condition means, expressed as percent of the NP alone score (i.e. NP minus SP/NP×100%; NP minus LP/NP×100%). The Raw Scores and Percent Change Scores were each analyzed by two-factor analysis of variance (ANOVA) with "Trial Type" as a within-subjects (repeated measures) factor and "Treatment" as a between-subjects factor. Subsequent individual comparisons were made using Dunnett's *t*-test for direct comparisons to vehicle controls. When necessary, LS means test was used to evaluate additional desired comparisons.

Drugs and injection parameters

All drugs were given intraperitoneally (IP). 5-HT releasing agents used were 3,4-methylenedioxymethamphetamine (MDMA) and fenfluramine. MDMA and fenfluramine were obtained from the National Institute of Drug Abuse (NIDA). Doses were chosen on the basis of previous work (Kehne et al. 1996b). Both releasers were racemic. (+)1-4-Iodo-2,5-dimethoxyphenyl-2-aminopropane (DOI; Research Biochemicals International) was tested in a dose-range in which it has demonstrated 5-$HT_{2A/2C}$ agonist activity in vivo using drug discrimination techniques (Glennon et al. 1986) and in which it disrupts prepulse inhibition (Sipes and Geyer 1994). MDL 100,907, *R*-(+)-a-(2,3-dimethoxyphenyl)-1-[2-(4-fluorophenylethyl)]-4-piperidinemethanol (Fig. 1) was synthesized at Hoechst Marion Roussel. The 2.0 mg/kg IP dose for use in experiments 1 and 2 was chosen on the basis of published studies evaluating the atypical antipsychotic activity of MDL 100,907 in rats (Sorensen et al. 1993; 1.0 mg/kg, IP, given chronically for 21 days; Moser et al. 1996; 1.0 mg/kg IP, significantly antagonized *d*-amphetamine disrupted latent inhibition and *d*-amphetamine stimulated locomotor activity). Haloperidol (Sigma) was administered in a dose (0.25 mg/kg) that is known from the literature to functionally block DA receptors (Geyer et al. 1990; Rigdon and Viik 1991), and yet which, on the basis of pilot studies in our lab, did not severely depress baseline startle.

Experimental protocols

In all experiments, rats were placed singly in a portable transport device modified from a standard lab rodent housing rack, and then moved from the animal rooms into the test rooms. They remained in these cages (including following pretreatment injections) until being placed in the startle apparatus for prepulse inhibition testing as described below.

Experiment 1: Fenfluramine and MDMA

These experiments used single doses of the selective 5-HT_{2A} antagonist MDL 100,907 or the D_2 antagonist haloperidol to evaluate the roles of 5-HT_{2A} or D_2 receptors, respectively, in mediating the disruptive effects of 20 mg/kg MDMA, or 5 mg/kg fenfluramine on auditory and/or visual prepulse inhibition in Wistar rats. Rats were injected with vehicle, 2.0 mg/kg MDL 100,907, or 0.25 mg/kg haloperidol and returned to their transport cages. Thirty minutes later, the rats were injected with vehicle, 20 mg/kg MDMA or 5 mg/kg fenfluramine, 15 min later were placed in the startle cages, and tested for prepulse inhibition for 11 min following a 5-min acclimation period.

Experiment 2: DOI

This study assessed the effects of DOI alone or in combination with MDL 100,907 or haloperidol on auditory and visual prepulse inhibition in Wistar rats. In the first experiment, rats were injected with vehicle or various doses of DOI (0.5–8 mg/kg), 15 min later were placed in the startle cages, and tested for prepulse inhibition for 11 min following a 5-min acclimation period. The second experiment used single doses of the selective 5-HT_{2A} antagonist MDL 100,907 or the D_2 antagonist haloperidol to evaluate the roles of 5-HT_{2A} or D_2 receptors, respectively, in mediating the disruptive effects of 2.0 mg/kg DOI on auditory and/or visual prepulse inhibition in Wistar rats. Rats were injected with vehicle, 2.0 mg/kg MDL 100,907, or 0.25 mg/kg haloperidol and returned to their transport cages. Thirty minutes later, the rats were injected with vehicle or 2.0 mg/kg DOI, 15 min later were placed in the startle cages, and tested for prepulse inhibition for 11 min following a 5-min acclimation period. The third experiment evaluated the effects of a range of doses of MDL 100,907 (0.00024–0.25 mg/kg) to estimate its potency in reversing DOI (2.0 mg/kg) disrupted auditory prepulse inhibition. Rats were injected with vehicle or 0.00024–0.25 mg/kg MDL 100,907. Thirty minutes later, the rats were injected with vehicle or 2.0 mg/kg DOI, 15 min later were placed in the startle cages, and tested for prepulse inhibition for 11 min following a 5 min acclimation period.

Fig. 2 Effects of IP administration of vehicle (*Veh*), haloperidol (*Hal*, 0.25 mg/kg), or MDL 100,907 (*MDL*, 2.0 mg/kg) 30 min prior to injection of vehicle or MDMA (20 mg/kg) on auditory or visual prepulse inhibition in Wistar rats. The *left panel* represents mean acoustic startle amplitude elicited in the absence of a prepulse (*filled bar*) or in the presence of an auditory prepulse (*open bar*) or visual prepulse (*diagonally hashed bar*). The *middle* and *right panels* represent the mean Change Scores (no prepulse condition minus prepulse condition) for the sound prepulse and light prepulse conditions. *Stars* represent significant differences from vehicle-injected controls. *Crosses* indicate significant difference from No Prepulse Condition

Results

Experiment 1: Fenfluramine and MDMA

Figure 2 and Table 1 shows the effects of vehicle, haloperidol (0.25 mg/kg), or MDL 100,907 (2.0 mg/kg) on the disruption of prepulse inhibition produced by 20

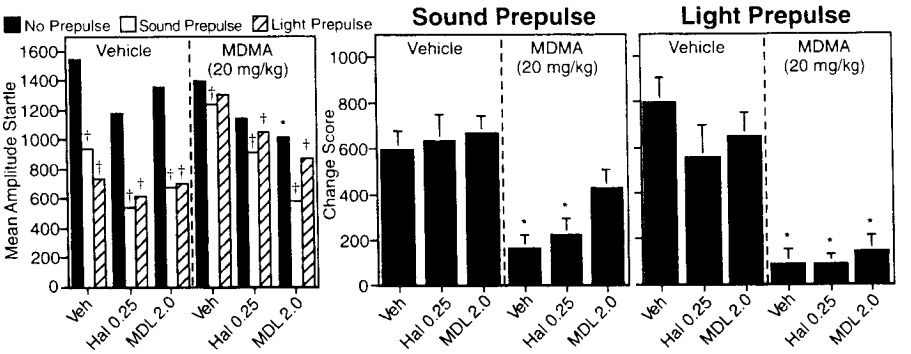


Table 1 Effects of MDL 100,907 (2.0 mg/kg and 0.00024–0.25 mg/kg), haloperidol (0.25 mg/kg), or vehicle on MDMA (20 mg/kg)-disrupted, fenfluramine (5.0 mg/kg)-disrupted, and/or DOI (2.0 mg/kg)-disrupted auditory and visual prepulse inhibition produced by in Wistar rats

Treatment A dose (mg/kg)	Treatment B dose (mg/kg)	*n*	No prepulse ±SEM (baseline)	Auditory			Visual		
				Pre-pulse	Change ±SEM	% Change ±SEM	Pre-pulse	Change ±SEM	% Change ±SEM
Vehicle	Vehicle	16	1546±86	942	602±78	42±6	743	803±103	53±6
Haloperidol 0.25	Vehicle	16	1184±129	545	639±110	56±7	623	561±133	47±9
MDL 100,907 2.0	Vehicle	16	1357±114	683	674±70	54±5	704	653±100	49±6
Vehicle	MDMA 20.0	16	1404±138	1240	164±60*	12±6*	1310	94±56*	3±5*
Haloperidol 0.25	MDMA 20.0	16	1146±134	917	229±63*	21±5	1054	92±40*	10±5*
MDL 100,907 2.0	MDMA 20.0	16	1018±155*	585	433±72	49±7	873	145±66*	18±11*
Vehicle	Vehicle	16	1149±127	831	318±57	25±8	819	330±61	33±7
Haloperidol 0.25	Vehicle	16	801±101	418	383±81	50±9	387	414±66	49±11
MDL 100,907 2.0	Vehicle	16	909±87	431	478±47	58±6	568	341±72	35±6
Vehicle	Fenfluramine 5.0	16	496±69*	418	78±78*	−5±20	426	70±57*	5±9
Haloperidol 0.25	Fenfluramine 5.0	16	354±83*	276	78±32*	23±9	298	56±36*	5±9
MDL 100,907 2.0	Fenfluramine 5.0	16	831±114	340	491±72	61±5	763	68±44*	13±6
Vehicle	Vehicle	16	1218±109	723	495±73	44±5	737	481±72	42±6
Haloperidol 0.25	Vehicle	16	957±113	535	422±56	50±6	540	417±82	49±7
MDL 100,907 2.0	Vehicle	16	1234±94	557	677±73	59±6	754	480±83	42±7
Vehicle	DOI 2.0	16	887±119	854	33±82*	−9±12*	494	393±68	45±8
Haloperidol 0.25	DOI 2.0	16	765±138*	811	−46±70*	−28±20*	444	321±72	47±7
MDL 100,907 2.0	DOI 2.0	16	837±137	372	465±114	54±8	435	402±102	48±10
Vehicle	Vehicle	16	1105±95	547	558±70	53±5	572	532±83	50 ±7
Vehicle	DOI 2.0	16	1062±97	829	234±72*	16±8*	746	316±79	28±7
MDL 100,907 0.00024	DOI 2.0	16	936±108	735	200±77*	8±13*	608	327±90	35±9
MDL 100,907 0.00098	DOI 2.0	16	1053±119	841	212±88*	19±9*	785	268±111*	21±9*
MDL 100,907 0.0039	DOI 2.0	16	1005±120	735	271±105*	19±10*	560	446±96	38±7
MDL 100,907 0.01563	DOI 2.0	16	929±82	578	351±85	41±9	552	377±74	43±7
MDL 100,907 0.0625	DOI 2.0	16	1076±96	643	433±104	34±8	631	446±71	44±6
MDL 100,907 0.25	DOI 2.0	16	998±100	507	490±71	54±8	550	447±67	49±8

* $P<0.05$ vs.Vehicle/Vehicle controls

mg/kg MDMA. MDL 100,907, but not haloperidol, attenuated the disruptive effect of MDMA on auditory prepulse inhibition, implicating the importance of 5-HT_{2A} receptors for this effect. Both MDL 100,907 and haloperidol failed to reverse the disruptive effect of fenfluramine or MDMA on visual prepulse inhibition. These conclusions were supported by a two-factor ANOVA of the Raw Scores which revealed a significant main effect of Trial Type, $F(2,180)=110.11$, $P<0.0001$, and a significant Trial Type×Treatment interaction, $F(10,180)=8.72$, $P<0.0001$. Dunnett's Test revealed significant auditory prepulse inhibition in all groups and significant visual prepulse inhibition in all groups except the vehicle/MDMA group. Baseline startle was significantly decreased in the MDL 100,907/MDMA group relative to the vehicle/vehicle controls. A two-factor ANOVA of the % Change Scores revealed significant main effects of Trial Type, $F(1,90)=10.20$, $P<0.0019$, and Treatment, $F(5,90)=10.91$, $P<0.0001$, and a significant interaction, $F(5,90)=4.02$, $P<0.0024$. Dunnett's test on the Change Scores and % Change Scores revealed significant differences in auditory prepulse inhibition for the vehicle/MDMA and haloperidol/MDMA (Change Scores only) groups, relative to the vehicle/vehicle controls. For visual prepulse inhibition, vehicle/MDMA, haloperidol/MDMA, and MDL 100,907/MDMA groups were all significantly different from the vehicle/vehicle controls.

Figure 3 and Table 1 shows the effects of vehicle, haloperidol (0.25 mg/kg), or MDL 100,907 (2.0 mg/kg) on the disruption of prepulse inhibition produced by 5.0 mg/kg fenfluramine. MDL 100,907, but not haloperidol, attenuated the disruptive effect of fenfluramine on auditory prepulse inhibition, implicating the importance of 5-HT_{2A} receptors for this effect. Neither agent restored the disruptive effect of fenfluramine on visual prepulse inhibition. These conclusions were supported by a two-factor ANOVA of the Raw Scores which revealed a significant main effect of Trial Type, $F(2,180)=89.16$, $P<0.0001$, and a significant Trial Type×Treatment interaction, $F(10,180)=9.36$, $P<0.0001$. Dunnett's test revealed significant auditory prepulse inhibition in all groups except vehicle/fenfluramine and haloperidol/fenfluramine, and significant visual prepulse inhibition in the vehicle/vehicle, haloperidol/vehicle, and MDL 100,907/vehicle groups. Baseline startle was significantly decreased in the vehicle/fenfluramine and haloperidol/fenfluramine groups relative to the vehicle/vehicle controls. A two-factor ANOVA of the % Change Scores revealed significant main effects of Trial Type, $F(1,90)=5.84$, $P<0.018$, and Treatment, $F(5,90)=6.86$, $P<0.0001$, and a significant Trial

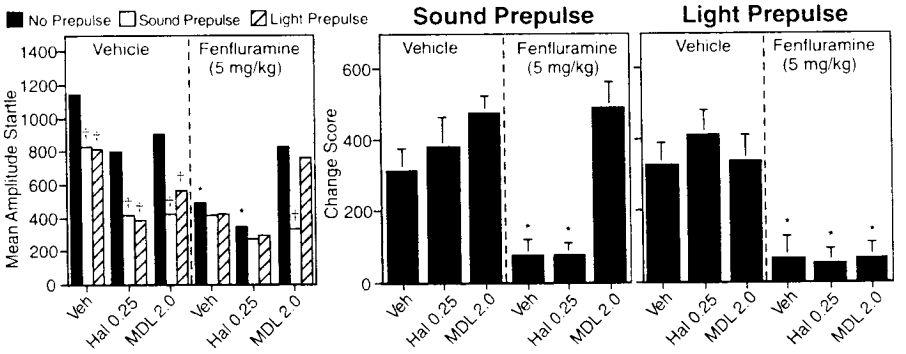


Fig. 3 Effects of IP administration of vehicle (*Veh*), haloperidol (*Hal*, 0.25 mg/kg), or MDL 100,907 (*MDL*, 2.0 mg/kg) 30 min prior to injection of vehicle or fenfluramine (5 mg/kg) on auditory or visual prepulse inhibition in Wistar rats. The *left panel* represents mean acoustic startle amplitude elicited in the absence of a prepulse (*filled bar*) or in the presence of an auditory prepulse (*open bar*) or visual prepulse (*diagonally hashed bar*). The *middle* and *right panels* represent the mean Change Scores (no prepulse condition minus prepulse condition) for the sound prepulse and light prepulse conditions. *Stars* represent significant differences from vehicle-injected controls. *Crosses* indicate significant differences from No Prepulse Condition

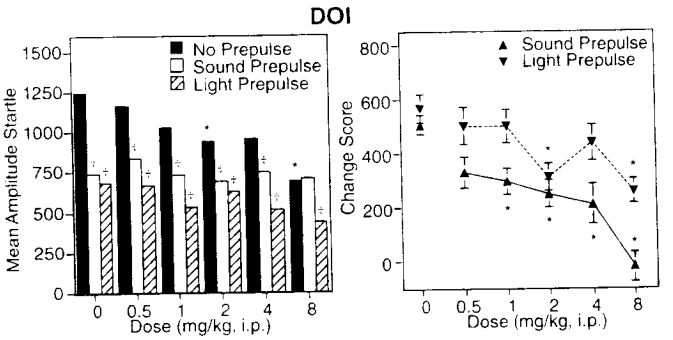


Fig. 4 Effects of IP administration of DOI (0.5–8.0 mg/kg) on auditory or visual prepulse inhibition in Wistar rats. The *left panel* represents the raw mean startle amplitudes for rats injected with vehicle or a selected dose of each compound. Each *bar* represents mean startle amplitude in the absence of a prepulse (*filled bar*), in the presence of a sound prepulse (*open bar*), or in the presence of a light prepulse (*diagonally hashed bar*). The *right panels* summarize the mean Change Score (no prepulse condition minus prepulse condition) for each dose group for auditory prepulse inhibition (*triangles with solid line*) or visual prepulse inhibition (*inverted triangles with dotted line*). *Stars* represent significant differences from vehicle-injected controls. *Crosses* indicate significant differences from No Prepulse Condition

Type×Treatment interaction, $F(5,90)=3.49$, $P<0.0063$. Dunnett's test of the Change Scores revealed significant differences in auditory prepulse inhibition for the vehicle/fenfluramine and haloperidol/fenfluramine groups, relative to the vehicle/vehicle controls. For visual prepulse inhibition, vehicle/fenfluramine, haloperidol/fenfluramine, and MDL 100,907/fenfluramine groups were all significantly different from the vehicle/vehicle controls. Dunnett's comparisons of % Change Scores were not significant.

Experiment 2: DOI

Figure 4 and Table 2 shows the dose-related effects of DOI on auditory and visual prepulse inhibition. This figure shows that DOI reduced auditory and visual prepulse inhibition in a dose-related manner, whereas the effect on visual prepulse inhibition was less clear in that it was not dose-related. A two-factor ANOVA of the Raw Scores revealed a significant main effect of Trial Type, $F(2,388)=171.42$, $P<0.0001$, a Treatment effect that approached statistical significance, $F(5,194)=1.99$, $P<0.081$, and a significant Trial Type×Treatment interaction, $F(10,388)=5.33$, $P<0.0001$. Dunnett's test revealed significant auditory prepulse inhibition at all doses except 8 mg/kg and significant visual prepulse inhibition at all doses. The 2 and 8 mg/kg doses significantly decreased baseline startle. A two-factor ANOVA of the % Change Scores revealed significant main effects of Trial Type, $F(1,194)=33.92$, $P<0.0001$, and of Treatment, $F(5,194)=6.01$, $P<0.0001$, and Trial Type×Treatment interaction that approached statistical significance, $F(5,194)=6.02$, $P<0.0001$. Dunnett's test on the Change Scores or % Change Scores revealed significant differences relative to vehicle-injected controls for auditory prepulse inhibition for the 1.0 (Change only), 2.0 (Change only), 4.0, and 8.0 mg/kg doses, and for the 2.0 and 8.0 (Change only) mg/kg doses for visual prepulse inhibition. These results support the conclusion that DOI consistently reduced auditory prepulse inhibition. The effect on visual prepulse inhibition was less clear in that it was not dose-related.

Figure 5 and Table 1 shows that the disruptive effect of 2.0 mg/kg DOI on auditory prepulse inhibition was antagonized by 2.0 mg/kg MDL 100,907 but not by 0.2 mg/kg haloperidol. These conclusions were supported by a two-factor ANOVA of the Raw Scores which revealed a significant main effect of Trial Type, $F(2,180)=97.28$, $P<0.0001$, and a significant interaction, $F(10,180)=7.67$, $P<0.0001$. Dunnett's test revealed significant auditory prepulse inhibition in all groups except vehicle/DOI and haloperidol/DOI. Significant visual prepulse inhibition was seen in all groups. Baseline startle was significantly decreased in the haloperidol/DOI group relative to the vehicle/vehicle controls. A two-factor ANOVA of the % Change Scores revealed significant main effects of Trial Type, $F(1,90)= 12.12$, $P<0.0008$, and Treatment, $F(5,90)=6.56$, $P<0.0001$, and a significant interaction, $F(5, 90)=9.76$, $P<0.0001$. Dunnett's Test's of the Change

Table 2 Effects of DOI (0.5–8.0 mg/kg) on auditory and visual prepulse inhibition in Wistar rats

5-HT agonist	Dose (mg/kg)	*n*	No prepulse ±SEM (baseline)	Auditory			Visual		
				Pre-pulse	Change ±SEM	% Change ±SEM	Pre-pulse	Change ±SEM	% Change ±SEM
DOI	Vehicle	40	1251±84	746	505±37	46±4	686	565±54	48±4
DOI	0.5	32	1172±91	844	328±56	30±4	673	499±69	48±5
DOI	1.0	32	1036±83	739	296±48*	30±6	538	498±62	49±5
DOI	2.0	32	944±74	695	249±52*	24±5	633	310±50*	28±8*
DOI	4.0	32	961±92	749	211±75*	2±16*	524	436±67	45±5
DOI	8.0	32	694±92*	714	−20±54*	−32±19*	437	258±46*	37±6

* $P<0.05$ vs.Vehicle controls

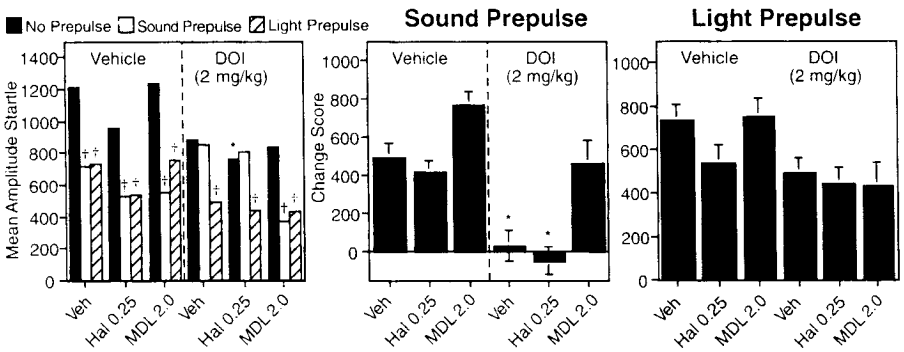


Fig. 5 Effects of IP administration of vehicle (*Veh*), haloperidol (*Hal*, 0.25 mg/kg), or MDL 100,907 (*MDL*, 2.0 mg/kg) 30 min prior to injection of vehicle or DOI (2 mg/kg) on auditory or visual prepulse inhibition in Wistar rats. The *left panel* represents mean acoustic startle amplitude elicited in the absence of a prepulse (*filled bar*) or in the presence of an auditory prepulse (*open bar*) or visual prepulse (*diagonally hashed bar*). The *middle* and *right panels* represent the mean Change Scores (no prepulse condition minus prepulse condition) for the sound prepulse and light prepulse conditions. *Stars* represent significant differences from vehicle-injected controls. *Crosses* indicate significant differences from No Prepulse Condition

Scores or% Change Scores revealed significant differences in auditory prepulse inhibition for the vehicle/DOI and haloperidol/DOI groups, relative to the vehicle/vehicle controls. For visual prepulse inhibition, no significant differences from the vehicle/vehicle controls were seen (in contrast to the significant disruption of 2 mg/kg seen above).

Figure 6 and Table 1 summarizes the effects of a range of doses of MDL 100,907 (0.00024–0.25 mg/kg) on the disruption of prepulse inhibition produced by 2.0 mg/kg DOI in rats. The top panel shows mean amplitude startle whereas the bottom panels show the Change Scores for auditory and visual prepulse inhibition. As seen from the Change Score data, MDL 100,907 dose-dependently antagonized the DOI disruption of auditory prepulse inhibition. A two-factor ANOVA of the Raw Scores revealed a significant main effect of Trial Type, $F(2,240)=92.93$, $P<0.0001$. Dunnett's test revealed significant auditory and visual prepulse inhibition in all groups. There were no statistically significant baseline effects. A two-factor ANOVA of the% Change Scores revealed significant effects of Trial Type, $F(1,120)=4.40$, $P<0.038$, and Treat-

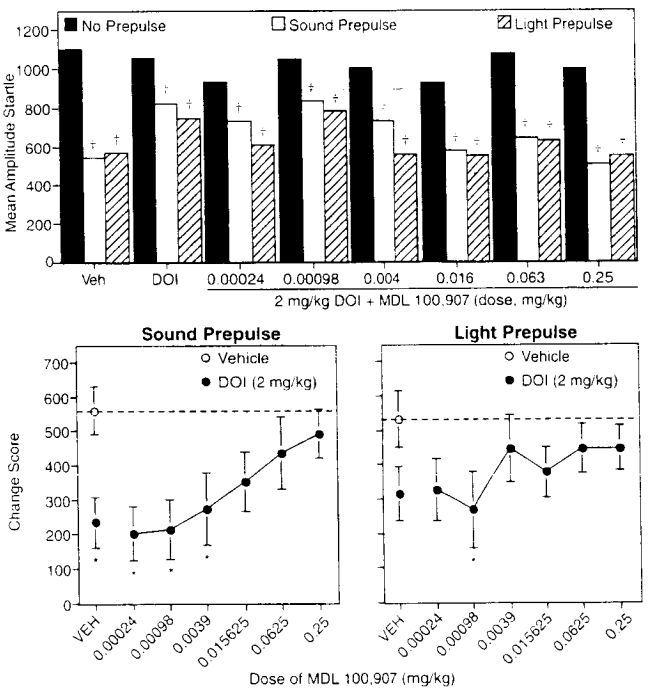


Fig. 6 Effects of a range of doses of MDL 100,907 (0.00024–0.25 mg/kg; 30 min pretreat) on DOI disruption of auditory or visual prepulse inhibition in rats. The *top panel* represents mean acoustic startle amplitude elicited in the absence of a prepulse (*filled bar*) or in the presence of an auditory prepulse (*open bar*) or visual prepulse (*diagonally hashed bar*). The *bottom panels* represent the mean Change Scores (no prepulse condition minus prepulse condition) for the sound prepulse and light prepulse conditions. *Asterisks* represent significant differences from vehicle/vehicle-injected controls (*open circles*). The *top graph* shows mean startle amplitude, whereas the *bottom panels* show the Change Scores for auditory and visual prepulse inhibition. *Crosses* indicate significant differences from No Prepulse Condition

ment, $F(7,120)=4.60$, $P<0.0001$. Dunnett's test revealed significant differences in auditory prepulse inhibition for the vehicle/DOI, the 0.00024 mg/kg MDL 100,907/DOI, 0.00098 mg/kg MDL 100,907/DOI and 0.0039 mg/kg MDL 100,907/DOI groups relative to the vehicle/vehicle controls. A significant difference in visual prepulse inhibition was seen for the 0.00098 mg/kg MDL 100,907/DOI group relative to vehicle/vehicle controls.

The ED_{50} for the MDL 100,907 reversal of DOI-disrupted auditory prepulse inhibition was estimated to be 0.04 mg/kg. An estimated ED_{100} dose was 0.1 mg/kg.

Discussion

The present studies found that the 5-HT_{2A} antagonist MDL 100,907 reversed the disruptions of auditory prepulse inhibition produced by MDMA, fenfluramine, and DOI, but did not consistently affect any observed disruptions in visual prepulse inhibition. Haloperidol did not reverse any of the disrupting effects of MDMA, fenfluramine, or DOI on prepulse inhibition. These data support the conclusion that MDMA, fenfluramine, and DOI disrupt auditory prepulse inhibition by stimulation of 5-HT_{2A} receptors, and these effects occur through a D_2 receptor-independent mechanism. The 5-HT receptors mediating the disruptive effects of 5-HT stimulation on visual prepulse inhibition are currently not known.

A key assumption in the single dose MDL 100,907 studies was that the 2.0 mg/kg dose (chosen on the basis of activities in various in vivo models) produced a selective blockade of 5-HT_{2A} receptors. Given the potency of MDL 100,907 in reversing DOI (ED_{50}=0.04 mg/kg; ED_{100}=0.1 mg/kg), this dose is approximately 20-fold higher than the ED_{100} dose. As described in the Introduction, there is a considerable separation of 5-HT_{2A} activity from activity at 26 other receptors as measured using in vitro binding studies (>100 fold separation from all other receptors measured), in vitro functional studies (>500 fold separation from activity at the 5-HT_{2C} receptor), and in vivo functional studies (>500 fold separation from activities at D_2 dopamine or a_1-adrenergic receptors). Recent ex vivo receptor binding studies have demonstrated that MDL 100,907 does not produce a significant occupation of α_1-adrenergic or D_2 dopaminergic receptors at doses of up to 10 mg/kg IP (P. van Giersbergen, and S. Sorensen, personal communication). Thus, MDL 100,907 probably had a selective action on 5-HT_{2A} receptors at the 2.0 mg/kg dose, though actions on other receptors cannot be currently ruled out.

Sipes and Geyer (1994) previously reported that the 5-HT_{2A}/α_1-adrenergic antagonist ketanserin reversed the disruptive effect of DOI on auditory prepulse inhibition. The present findings with MDL 100,907 extend these findings to include the Wistar strain, and strengthen the involvement of 5-HT_{2A} receptors in that MDL 100,907 is a more selective 5-HT_{2A} antagonist relative to ketanserin. The most notable difference is that MDL 100,907 lacks significant binding activity at the α_1-adrenergic receptor (Leysen et al. 1993; Palfreyman et al. 1993; Kehne et al. 1996a).

In addition to stimulating 5-HT_{2A} receptors, DOI possesses 5-HT_{2C} agonist activity. Sipes and Geyer (1994) found that the 5-HT_{2C} agonist mCPP did not block auditory prepulse inhibition, suggesting that 5-HT_{2C} receptors are not important for the disrupting effect of DOI on auditory prepulse inhibition. Another approach to evaluating the potential contribution of 5-HT_{2C} receptors to DOI's effects would be to demonstrate that DOI-disrupted auditory prepulse inhibition is not antagonized by a selective 5-HT_{2C} antagonist.

As reported previously (Kehne et al. 1996b), the 5-HT releasers MDMA and fenfluramine disrupted visual prepulse inhibition. The disruptions of both auditory and visual prepulse inhibition produced by fenfluramine were previously shown to be serotonergically mediated (Kehne et al. 1996b). The present study reports the novel finding that MDL 100,907 was not effective in reversing these disruptions, suggesting that, at least for fenfluramine, 5-HT receptor subtypes other than 5-HT_{2A}must be involved. Previous data demonstrated involvement of 5-HT_{1A} receptors (Rigdon and Weatherspoon 1992; Sipes and Geyer 1995) and 5-HT_{1B} receptors (Sipes and Geyer 1994) in the modulation of auditory prepulse inhibition in rats. Further studies are needed to evaluate the contribution of these and other 5-HT receptor subtypes to 5-HT releaser-disrupted visual prepulse inhibition, as well as precisely identifying the anatomical site(s) of action. More generally, these results highlight the potential utility of incorporating multiple prepulse sensory modalities within the same experiment.

Deficits in prepulse inhibition have been measured in schizophrenics (Braff and Geyer 1989; Geyer et al. 1990; Grillon et al. 1992; Judd et al. 1992; Karper et al. 1993), and the importance of 5-HT_{2A} receptors to the mechanism of action of many antipsychotic drugs has been suggested (Meltzer et al. 1989; Meltzer 1991; Schmidt et al. 1993). In the present study, haloperidol was not effective in normalizing the disruptions of prepulse inhibition produced by any of the 5-HT agents, indicating that these effects may occur independently of D_2 dopaminergic receptor stimulation. Recent studies in which multivariate analyses have been performed on postmortem neurochemical profiles of the brains of schizophrenics have revealed a subpopulation of schizophrenics characterized by excess serotonergic activity (Hansson et al. 1994). Furthermore, approximately one-fourth of the schizophrenic population does not respond to classic neuroleptics such as haloperidol. If excessive 5-HT_{2A} overactivity contributes to the neurochemical imbalance in this population or a subset thereof, then MDL 100,907 might be expected to be useful in normalizing such an imbalance. Such speculation remains to be tested.

It should be emphasized that deficits in prepulse inhibition have been measured in CNS disorders other than schizophrenia, including Huntington's disease (Swerdlow et al. 1995) and obsessive compulsive disorder (Swerdlow et al. 1993). While the neurochemical bases for these

effects are not fully understood, the present preclinical studies suggest the possibility that MDL 100,907 may be generally useful in any CNS disorder in which excess 5-HT_{2A} receptor tone disrupts sensory gating processes.

In summary, the present studies demonstrated that MDL 100,907 reversed the disruptions of auditory prepulse inhibition produced by the 5-HT releasers MDMA or fenfluramine, or by the 5-$HT_{2A/2C}$ agonist DOI, and these effects were independent of D_2 dopamine receptors. These studies support the continued development of MDL 100,907 as a novel atypical antipsychotic, and warrant the further evaluation of prepulse inhibition as an in vivo model for measuring sensorimotor gating processes.

Acknowledgements Much of these data were submitted by R.A.P. as part of a PhD dissertation at the University of Cincinnati. The authors especially thank Drs Marvin Schwartz, Christopher Schmidt, Stephen Sorensen, and Janice Hitchcock for their helpful feedback during the course of these studies.

References

Appel NM, Mitchell WM, Garlick RK, Glennon RA, Teiteler M, DeSouza EB (1990) Autoradiographic characterization of (+)-1-(2,5-dimethoxy-4-[^{125}I]iodophenyl)-2-aminopropane ([^{125}I]DOI) binding to 5-HT_2 and 5-HT_{1C} receptors in rat brain. J Pharmacol Exp Ther 255: 843–857

Berger UV, Gu XF, Azmitia EC (1992) The substituted amphetamines 3,4-methyledioxymethamphetamine, methamphetamine, *p*-chloroamphetamine, and fenfluramine induce 5-hydroxytryptamine release via a common mechanism blocked by fluoxetine and cocaine. Eur J Pharmacol 215: 153–160

Braff DL, Geyer MA (1989) Sensorimotor gating and the neurobiology of schizophrenia: Human and animal model studies. In: Schultz S, Tamminga C (eds) Schizophrenia: scientific progress. Oxford University Press, NY, pp 124–136

Breier A (1995) Serotonin, schizophrenia and antipsychotic drug action. Schizophr Res 14: 187–202

Geyer MA, Swerdlow NS, Mansbach RS, Braff DL (1990) Startle response models of sensorimotor gating and habituation deficits in schizophrenia. Brain Res Bull 25: 485–498

Glennon RA (1986) Discriminative stimulus properties of the serotonergic agent 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). Life Sci 39: 825–830

Glennon RA, Titeler M, Young R (1986) Structure-activity relationships and mechanism of action of hallucinogenic agents based on drug discrimination and radioligand binding studies. Psychopharmacol Bull 22: 953–958

Grillon C, Ameli R, Charney DS, Krystal J, Braff DL (1992) Startle gating deficits occur across prepulse intensities in schizophrenic patients. Biol Psychiatry 32: 939–943

Hansson LO, Waters N, Winblad B, Gottfries CG, Carlsson A (1994) Evidence for biochemical heterogenity in schizophrenia: a multivariate study of monoaminergic indices in human post-mortal brain tissue. J Neural Trans – [Gen Sect] 98: 217–235

Hoffman HS, Ison JR (1980) Reflex modification in the domain of startle: I. Some empirical findings and their implications for how the nervous system processes sensory input. Psychol Rev 87: 175–189

Judd LL, McAdams L, Budnick B, Braff DL (1992) Sensory gating deficits in schizophrenia: new results. Am J Psychiatry 4: 488–493

Karper LP, Freeman GK, Morgan CA, Grillon C, Charney DS, Krystal JH (1993) Prepulse inhibition of the acoustic startle response and measures of attention in schizophrenic subjects. Schizophrenia Res 9: 160

Kehne JH, McCloskey TC, Taylor VL, Black CK, Fadayel GM, Schmidt CJ (1992) Effects of the serotonin releasers 3,4-methylenedioxymethamphetamine (MDMA), 4-chloroamphetamine (PCA) and fenfluramine on acoustic and tactile startle reflexes in rats. J Pharmacol Exp Ther 260: 78–89

Kehne JH, Baron BM, Carr AA, Chaney SF, Elands J, Feldman DJ, Frank RA, van Giersbergen PLM, McCloskey TC, Johnson MP, McCarty DR, Poirot M, Senyah Y, Siegel BW, Widmaier C (1996a) Preclinical characterization of the potential of the putative atypical antipsychotic MDL 100,907 as a potent and selective 5-HT_{2A} antagonist with a favorable CNS safety profile. J Pharmacol Exp Ther (in press)

Kehne JH, Padich RA, McCloskey TC, Taylor VL, Schmidt CJ (1996b) 5-HT modulation of auditory and visual sensorimotor gating: I. Effects of 5-HT releasers on sound and light prepulse inhibition in Wistar rats. Psychopharmacology 124: 95–106

Leysen JE, Janssen PMF, Schotte A, Luyten WHML, Megens AAHP (1993) Interaction of antipsychotic drugs with neurotransmitter receptor sites in vitro and in vivo in relation to pharmacological and clinical effects: role of 5HT_2 receptors. Psychopharmacology 112: S40–S54

Mansbach RS (1991) Effects of NMDA receptor ligands on sensorimotor gating in the rat. Eur J Pharmacol 202: 61–66

Mansbach RS, Geyer MA, Braff DL (1988) Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacology 94: 507–514

Mansbach RS, Braff DL, Geyer MA (1989) Prepulse inhibition of the acoustic startle response is disrupted by N-ethyl-3,4-methylenedioxymethamphetamine (MDEA) in the rat. Eur J Pharmacol 167: 49–55.

Marek GJ, Aghajanian GK (1994) Excitation of interneurons in piriform cortex by 5-hydroxytryptamine: blockade by MDL 100,907, a highly selective 5-HT_{2A} receptor antagonist. Eur J Pharmacol 259: 137–141

Meltzer H (1991) Effects of antipsychotic drugs on serotonin receptors. Pharmacol Rev 43: 587–604

Meltzer H, Matzubara S, Lee J (1989) Classification of typical and atypical antipsychotic drugs on the basis of dopamine D_1, D_2 and serotonin$_2$ pKi values. J Pharmacol Exp Ther 251: 238–246

Moser PC, Moran PM, Frank RA, Kehne JH (1996) Reversal of amphetamine-induced behaviours by MDL 100,907, a selective 5-HT_{2A} antagonist. Behav Brain Res 13:163–167

Palfreyman MG, Schmidt CJ, Sorensen SM, Dudley MW, Kehne JH, Moser P, Gittos MW, Carr AA (1993) Electrophysiological, biochemical, and behavioral evidence for 5-HT_2 and 5-HT_3 mediated control of dopaminergic function. In: Kahn Rs (ed) Proceedings of American College of Neuropsychology Symposium. Psychopharmacology 112: S60–S67

Peroutka SJ (1994) Molecular biology of serotonin (5-HT) receptors. Synapse 18: 241–260

Pranzatelli MR (1990) Evidence for involvement of 5HT_2 and 5-HT_{1C} receptors in the behavioral effects of the 5-HT agonist 1-(2,5-dimethoxy-4-iodophenyl aminopropane)-2 (DOI). Neurosci Lett 115: 74–80

Rigdon GC, Viik K (1991) Prepulse inhibition as a screening test for potential antipsychotics. Drug Dev Res 23: 91–99

Rigdon GC, Weatherspoon JK (1992) 5-Hydroxytryptamine$_{1A}$ receptor agonists block prepulse inhibition of acoustic startle reflex. J Pharmacol Exp Ther 263: 486–493

Schmidt CJ, Kehne JH (1990) Neurotoxicity of MDMA: neurochemical effects. In: The neuropharmacology of serotonin. Ann NY Acad Sci 600: 665–681

Schmidt CJ, Taylor VL (1990) Reversal of the acute effects of 3,4-methylenedioxymethamphetamine by 5-HT uptake inhibitors. Eur J Pharmacol 181: 133–136

Schmidt CJ, Kehne JH, Carr AA, Fadayel GM, Humphreys TM, Ketteler HJ, McCloskey TC, Padich RA, Taylor VL, Sorensen SM (1993) Contribution of serotonin neurotoxins to understanding psychiatric disorders: the role of 5-HT_2 receptors in schizophrenia and antipsychotic activity. Int Clin Psychopharmacol 8 [Suppl. 2] 25–32

Schmidt CJ, Sorensen SM, Kehne JH, Carr AA, Palfreyman MG (1995) The role of 5-HT_{2A} receptors in antipsychotic activity. Life Sci 56: 2209–2222

Sipes TA, Geyer MA (1994) Multiple serotonin receptor subtypes modulate prepulse inhibition of the startle response in rats. Neuropharmacology 33: 441–448

Sipes TA, Geyer MA (1995) 8-OH-DPAT disruption of prepulse inhibition in rats: reversal with (+)WAY 100,135 and localization of site of action. Psychopharmacology 117: 41–48

Sorensen SM, Kehne JH, Fadayel GM, Humphreys TM, Ketteler HJ, Sullivan CK, Taylor VL, Schmidt CJ (1993) Characterization of the 5-HT_2 receptor antagonist MDL 100,907 as a putative antipsychotic: Behavioral, electrophysiological and neurochemical studies. J Pharmacol Exp Ther 266: 684–691

Swerdlow NR, Mansbach RS, Geyer MA, Pulvirenti L, Braff DL (1990) Amphetamine disruption of prepulse inhibition of acoustic startle is reversed by depletion of mesolimbic dopamine. Psychopharmacology 100: 413–416

Swerdlow NR, Keith VA, Braff DL, Geyer MA (1991) Effects of spiperone, SCH 23390, and clozapine on apomorphine inhibition of sensorimotor gating of the startle reflex in the rat. J Pharmacol Exp Ther 256: 530–536

Swerdlow NR, Benbow CH, Zisook S, Geyer MA, Braff DL (1993) A preliminary assessment of sensorimotor gating in patients with obsessive compulsive disorder. Biol Psychiatry 33: 298–301

Swerdlow NR, Paulsen J, Braff D.L, Butters N, Geyer MA, Swenson MR (1995) Impaired prepulse inhibition of acoustic and tactile startle response in patients with Huntington's disease. J Neurol Neurosurg Psychiatry 58: 192–200

Titeler M, Lyon RA, Davis KH, Glennon RA (1987) Selectivity of serotonergic drugs for multiple brain serotonin receptors. Biochem Pharmacol 36: 3265–3271

Note added in proof Varty and Higgins (Psychopharmacology 122: 15–26, 1995) reported that clozapine and risperidone, antipsychotics with demonstrated 5-HT_2 antagonist activity, reversed DOI-disrupted auditory prepulse inhibition, whereas haloperidol and raclopride, antipsychotics with predominantly D_2 antagonist profiles, were without effect. These results support the present findings of differential effects of MDL 100,907 and haloperidol on DOI, MDMA, or fenfluramine-disrupted auditory prepulse inhibition.