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ORIGINAL INVESTIGATION

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Serotonin releasers increase prepulse inhibition in serotonin 1B knockout mice

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Abstract *Rationale:* Prepulse inhibition (PPI) is the normal reduction of the startle response which occurs when an abrupt startling stimulus is preceded by a weak pre-stimulus and is decreased in several neuropsychiatric disorders. *Objective:* The role of the serotonin 1B (5-HT_{1B}) receptor in modulating PPI was investigated using 5-HT-releasing agents in wild-type (WT) and 5-HT_{1B} knockout (1BKO) mice. Whether the differential effects of 5-HT-releasing agents on PPI in WT and 1BKO mice resulted from lack of the 5-HT_{1B} receptor or altered development was also assessed. *Methods:* PPI was assessed in WT and 1BKO mice treated with the 5-HT-releasing agents (+)3,4-methylenedioxy-*N*-methylamphetamine (MDMA: 0, 10 mg/kg) or (±)*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB: 0, 10 mg/kg). Additionally, intact 129 Sv mice received pre-treatments of the 5-$HT_{1B/1D}$ antagonist GR 127935 (0, 0.75, 1.5, 3.0 mg/kg) and treatments of MDMA (10 mg/kg). *Results:* MDMA and MBDB increased PPI in 1BKO mice, but did not alter PPI in WT mice. Intact 129 Sv mice receiving 3.0 mg/kg GR 127935 and 10 mg/kg MDMA exhibited increases in PPI. *Conclusions:* The ability of GR 127935 to increase PPI in intact MDMA-treated mice suggests that lack of the 5-HT_{1B} receptor, and not altered development, is responsible for the PPI-increasing effects of 5-HT releasers in 1BKO mice. 5-HT release activates multiple 5-HT receptor subtypes, which individually may increase or decrease PPI and together have a combined effect on PPI. Our finding that MDMA and MBDB increase PPI in 1BKO, but not WT mice, indicates that the activation of 5-HT_{1B} receptors by 5-HT disrupts PPI.

Key words Startle · Sensorimotor gating · Serotonin 1B receptor · MBDB · MDMA · GR 127935

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Introduction

Prepulse inhibition (PPI) is the reduction in magnitude of the startle reflex that occurs when an abrupt startling stimulus is preceded 30–500 ms by a pre-stimulus or "prepulse". PPI provides an operational measure of sensorimotor gating, which is a neural mechanism theorized to maintain mental and behavioral integration by inhibiting extraneous sensory and cognitive information and motor programs. PPI is reduced in patients with several neuropsychiatric disorders including schizophrenia (Braff et al. 1978, 1992; Grillon et al. 1992; Bolino et al. 1994), obsessive compulsive disorder (OCD) (Swerdlow et al. 1993), Tourette's syndrome (Castellanos et al. 1991), and Huntington's disease (Swerdlow et al. 1995). People with these disorders report inundation of sensory stimuli, thoughts, and/or exhibit motor disinhibition. Because the serotonin (5-HT) system has been implicated in the pathophysiology of schizophrenia and OCD (Meltzer 1995, 1997), dissecting its role in PPI could provide insight into the pathophysiology of these disorders.

The modulation of PPI by the serotonergic system has received much recent attention. Experiments using wild-type (WT) and 5-HT_{1B} knockout (1BKO) mice show that the direct 5-$HT_{1A/1B}$ agonist RU24969 decreases PPI in WT but not in 1BKO mice, suggesting that the activation of the 5-HT_{1B} receptor decreases PPI (Dulawa et al. 1997, 1998). Rats treated with RU24969 also exhibit disruptions of PPI (Sipes and Geyer 1994, 1996), although these results cannot be attributed specifically to the 5-HT_{1B} receptor. The 5-HT_{1B} receptor is found in both mice and in humans (Hartig et al. 1996), and functions as

a terminal autoreceptor that inhibits neurotransmitter release for 5-HT-containing neurons (Middlemiss 1984; Engel et al. 1986; Johanning et al. 1992) and as a terminal postsynaptic receptor for neurons containing other neurotransmitters (Wu et al. 1991; Hen 1992; Bennett-Clarke et al. 1993; Boschert et al. 1994). The 5-HT_{1B} receptor is localized densely in brain regions that have been shown to be critically involved in the modulation of PPI, such as striatal GABAergic (γ-aminobutyric acid type) terminals in the ventral pallidum and the ventral tegmental area/substantia nigra (VTA/SN) (Pazos et al. 1988; Boschert et al. 1994). The role of the 5-HT_{1B} receptor in modulating PPI has thus far been studied in mice only with the use of a direct agonist. It is also important to study the role of this receptor using indirect agonists, which more closely mimic physiological conditions.

The methylenedioxy-substituted phenalkylamines 3,4-methylenedioxy-*N*-methylamphetamine (MDMA), (±)*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB), and related compounds are potent releasers of presynaptic 5-HT with varying potencies as dopamine releasers (Johnson et al. 1986; Hekmatpanah and Peroutka 1990) and monoamine uptake blockers (Nichols 1986; Johnson et al. 1987). MDMA releases 5-HT and releases dopamine to a lesser degree in vitro (Schmidt 1987), while MBDB releases 5-HT and has little influence on catecholamine release (Johnson et al. 1986). MDMA, MBDB, and related agents induce behavioral effects that are distinct from those of both phenylalkylamine psychostimulants and classical hallucinogens (Glennon et al. 1988; Oberlander and Nichols 1988; Geyer and Callaway 1994). These effects include powerful increases in emotional sensitivity, empathy, and affiliative bonds with other people (Anderson et al. 1978; Shulgin 1978; Nichols 1986; Nichols et al. 1986; Geyer and Callaway 1994). Because MDMA and MBDB are potent releasers of presynaptic 5-HT, they can be used as pharmacological tools to better understand the role of central serotonergic systems in behaviors of interest (Geyer and Callaway 1994).

We used indirect 5-HT agonists, which conserve normal physiological relationships between 5-HT release and receptors (unlike direct agonists), to explore the consequences of 5-HT_{1B} receptor activation on PPI. The present experiments investigated effects of the 5-HT releasers MDMA and MBDB on PPI in WT and 1BKO mice. Because constitutive knockout manipulations can lead to developmental changes, we also assessed the effects of MDMA in intact mice treated with the 5-$HT_{1B/1D}$ antagonist GR 127935. Finding the same effect of MDMA in GR 127935-treated intact mice and 1BKO mice would implicate the lack of the 5-HT1B receptor in the effect. However, finding different effects of MDMA would implicate altered development in the results obtained with 1BKO mice. Both genotypes received treatments of MDMA (0, 10 mg/kg) or MBDB (0, 10 mg/kg) in two separate experiments. Because both compounds increased PPI in 1BKO mice and had no effect in WT mice, we undertook studies with GR 127935 (0, 0.75, 1.5, and 3.0 mg/kg) to determine whether the increase in PPI in 1BKO mice resulted from lack of the 5-HT_{1B} receptor or from altered development.

Methods

Animals

WT and 1BKO mice on a pure 129 Sv background (Phillips et al. 1999) were received from Columbia University, New York, N.Y. WT and 1BKO mice were the offspring of either heterozygote breeders or homozygote breeders no more than three generations removed from a heterozygote cross. Intact 129SvEms-+^{Ter}?/J mice were obtained from Jackson Labs (Bar Harbor, Me.). All mice weighed 20–35 g and were 7–12 weeks of age at the time of testing. Animals were housed in groups of four with same-type mice and were maintained on a 12-h/12-h light/dark schedule (lights on at 1700 hours) with food and water provided ad libitum. Behavioral testing occurred between 0800 hours and 1800 hours, because acoustic startle is more robust and less variable during the dark circadian phase (Davis and Sollberger 1971). Animal testing was conducted in accord with the *Principles of laboratory animal care* National Institutes of Health (NIH) guidelines and local animal care committee guidelines.

Apparatus

Startle chambers (SR-LAB, San Diego Instruments, San Diego, Calif.) consisted of nonrestrictive Plexiglas cylinders, 5 cm in diameter, resting on a Plexiglas platform in a ventilated and well-lit chamber. A high-frequency speaker mounted 33 cm above the cylinder produced all acoustic stimuli. A piezoelectric accelerometer mounted under each cylinder detected and transduced animal movements. A computer and interface assembly digitized and stored the data. To obtain the amplitude of the animals' startle response to each stimulus, 65 consecutive 1-ms readings were collected beginning at stimulus onset. A dynamic calibration system (San Diego Instruments) was used to ensure comparable sensitivities across chambers. Sound levels were measured in dB(A) SPL as described elsewhere (Geyer and Swerdlow 1998).

Drugs

All injections were given using 0.5-cc insulin syringes and 28-gauge needles. Solutions were prepared at a volume of 5 ml/kg body weight. (+)3,4-methylenedioxy-*N*-methylamphetamine (MDMA) (National Institute on Drug Abuse, Bethesda, Md.) was injected i.p. (±)*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB) was provided by Dr. David Nichols, Purdue University (Nichols et al. 1986) and was injected s.c. GR 127935 (Glaxo, Middlesex, UK) was injected i.p. MDMA and MBDB were dissolved in 0.9% saline, while GR 127935 was dissolved in water.

Test session

Five different trial types were presented in the test session: a 40-ms broadband 120-dB burst (pulse-alone trial); three different prepulse + pulse trials in which 20-ms long 3-dB (pp3p120), 6-dB (pp6p120), or 12-dB (pp12p120) stimuli above a 65-dB background preceded the 120-dB pulse by 100 ms (onset to onset); and a no-stimulus trial, in which only the background noise was presented. Thus, the five trial types presented were: pulse alone; pp3p120; pp6p120; pp12p120; and no stimulus. Trials were presented in a pseudo-random order. An average of 15 s (range 7–23 s) separated trials.

The test session consisted of 62 test trials. The session began with a 5-min acclimation period, followed by four consecutive blocks of test trials. Blocks one and four consisted of six consecutive pulse-alone trials, while blocks two and three contained six pulse-alone trials, five pp3p120 trials, five pp6p120 trials, five pp12p120 trials, and four no-stimulus trials.

Behavioral testing

Studies were conducted using separate groups of animals and between-subject designs. In the first experiment, 11 WT and 10 1BKO male mice received saline or 10 mg/kg MDMA 15 min before startle testing. In the second experiment, 20 WT and 19 1BKO female mice received treatments of either saline or 10 mg/kg MBDB and were placed into testing chambers 15 min after injection. The 10-mg/kg doses were selected based on the results of dose–response experiments of MDMA and MBDB (0, 5, 10, or 20 mg/kg), in which 20 mg/kg significantly altered startle magnitude, but no other doses affected PPI or startle magnitude (data not shown). In the third experiment, 36 129 Sv female mice received 10 mg/kg MDMA and one dose of GR 127935 (0, 0.75, 1.5, or 3.0 mg/kg) 20 min before startle testing (10 mg/kg MDMA had no effect on PPI in WT animals).

Data analysis

The effects of genotype, drug treatment, and prepulse intensity on PPI were evaluated using multi-way analyses of variance (ANOVAs). Genotype and drug treatment were assessed as between-subject factors and prepulse intensity was assessed as a within-subjects factor. Newman-Keul's post-hoc comparisons were applied when interactions or main effects of drug were observed. The criterion for significance for all analyses was $P<0.05$.

PPI was calculated as the averaged startle magnitude on pulse-alone trials from blocks two and three, minus the averaged startle magnitude on prepulse/pulse trials, all divided by the averaged pulse-alone values from blocks two and three. The resulting value was multiplied by 100, then subtracted from 100 to be presented as a percentage PPI value. Block-one startle magnitude values were not used in the calculation of PPI because they reflect the initial rapid habituation of startle and are highly variable. Block-four startle values were not used because they are not intermixed with the prepulse + pulse trials as in blocks two and three.

Startle reactivity was evaluated by comparing the averaged values from blocks two and three. This procedure served to determine whether changes in startle reactivity confounded the assessment of PPI. Two-factor ANOVAs were applied with genotype and drug as between-subject factors. Newman Keul's post-hoc tests were applied when interactions or main effects of drug were observed.

Results

MDMA

The effects of 10 mg/kg MDMA on startle reactivity in WT mice and 1BKO mice are shown in Fig. 1a. Analysis revealed main effects of genotype ($F_{1,17}$=23.77, $P<0.001$) and drug ($F_{1,17}$=5.05, $P<0.05$), and an interaction of genotype and drug ($F_{1,17}$=15.09, $P<0.01$). Newman Keul's post-hoc comparisons indicated that 1BKO mice treated with 10 mg/kg MDMA had significantly lower startle magnitude values than all other groups of mice.

A three-way ANOVA revealed main effects of genotype ($F_{1,17}$=8.79, $P<0.01$), drug ($F_{1,17}$=5.92, $P<0.05$), and prepulse intensity ($F_{2,34}$=138.88, $P<0.01$). Analysis also revealed a genotype × prepulse intensity interaction ($F_{2,34}$=4.34, $P<0.05$) and a genotype × drug × prepulse intensity interaction ($F_{2,34}$=3.25, $P<0.05$). Newman Keul's post-hoc tests revealed that MDMA-treated 1BKO mice had significantly higher PPI levels than all other groups of mice at the 6-dB prepulse intensity. Thus, 10 mg/kg MDMA increased PPI in 1BKO mice at the 6-dB prepulse intensity and had no effect in WT mice (Fig. 1b).

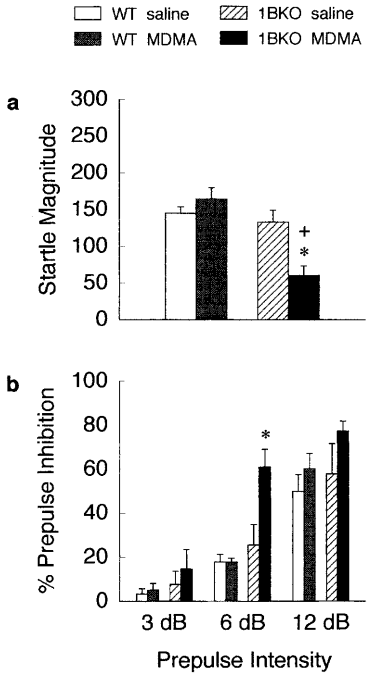

Fig. 1a, b Values represent mean±SEM for wild-type (WT) and 5-HT_{1B} knockout (1BKO) mice treated with saline or 10 mg/kg (+)3,4-methylenedioxy-*N*-methylamphetamine (MDMA). **a** Startle magnitude is shown. **b** Percentage prepulse inhibition (PPI) is shown. An *asterisk* indicates that the group mean is significantly different from the same genotype saline value; + indicates that the group mean is significantly different from same drug-treated mice of the other genotype ($P<0.05$)

MBDB

The effects of 10 mg/kg MBDB on startle reactivity in WT and 1BKO mice are shown in Fig. 2a. A two-factor ANOVA assessed the effects of genotype and MBDB on startle magnitude in blocks two and three. Analysis revealed a main effect of genotype ($F_{1,35}$=6.09, $P<0.05$). No main effect of drug or interactions were observed.

A three-way ANOVA revealed a main effect of genotype ($F_{1,35}$=7.03, $P<0.02$) and a trend for a genotype × drug interaction ($F_{1,35}$=3.73, P=0.06). Post-hoc tests were based on this trend and the a priori hypothesis that 5-HT releasers increase PPI in 1BKO mice derived from experiment one. Newman-Keul's post-hoc tests indicated that 1BKO mice treated with 10 mg/kg MBDB had sig-

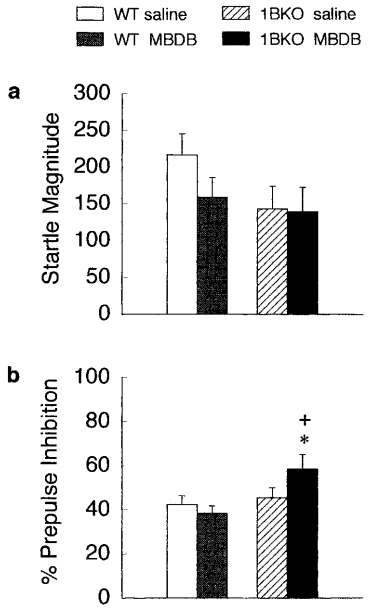

Fig. 2 **a** Startle magnitude for wild-type (WT) and 5-HT_{1B} knockout (1BKO) mice treated with saline or 10 mg/kg (±)*N*-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine (MBDB). **b** Percentage prepulse inhibition (PPI) values are shown, averaged across prepulse intensities. An *asterisk* indicates that the group mean is significantly different from the same genotype saline value; + indicates that the group mean is significantly different from same drug-treated mice of the other genotype

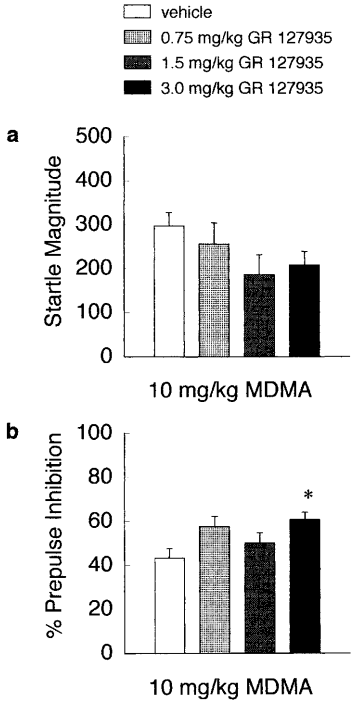

Fig. 3 **a** Startle magnitude for 129 Sv mice treated with 10 mg/kg (+)3,4-methylenedioxy-*N*-methylamphetamine (MDMA) and 0, 0.75, 1.5, or 3.0 mg/kg GR 127935. **b** Percentage prepulse inhibition (PPI) values are shown, averaged across prepulse intensities. An *asterisk* indicates that the group mean is significantly different from 0 mg/kg GR 127935

nificantly higher PPI levels than all other groups of mice (Fig. 2b).

MDMA and GR 127935

A one-factor ANOVA assessed the effects of GR 127935 on startle magnitude in blocks two and three. MDMA was not a factor in the analysis because all animals received MDMA. Because no effect of 10 mg/kg MDMA was found in WT 129 Sv mice in experiment one or in previous experiments (Dulawa and Geyer 1998; Dulawa and Geyer, unpublished observations), animals were used to test more doses of GR 127935 rather than to replicate this negative finding. Analysis revealed no main effect of drug on startle magnitude (Fig. 3a).

A two-way ANOVA comparing the effects of GR 127935 and prepulse intensity on PPI revealed main effects of drug ($F_{3,32}$=3.33, P<0.04) and prepulse intensity ($F_{2,64}$=150.90, P<0.001), and no interactions. Newman-Keul's post-hoc tests indicated that mice treated with 10 mg/kg MDMA and 3.0 mg/kg GR 127935 had higher PPI levels than mice treated with 10 mg/kg MDMA and vehicle (Fig. 3b).

Discussion

The 5-HT-releasing agents MDMA and MBDB increased PPI in 1BKO mice, but had no effect in WT mice in the present experiments. In addition, the 5-$HT_{1B/1D}$ antagonist GR 127935 produced increases in PPI relative to vehicle in intact MDMA-treated mice. Several conclusions can be drawn from these results. One, the release of 5-HT induced by MDMA and MBDB does not alter PPI in intact mice of this 129 Sv substrain. Two, the increase in PPI induced by 5-HT releasers in 1BKO mice probably resulted from lack of the 5-HT_{1B} receptor rather than altered development, because MDMA increased PPI in GR 127935-treated mice. Three, the differential effects of 5-HT releasers in WT and 1BKO mice indicate that the activation of 5-HT_{1B} receptors by 5-HT decreases PPI.

5-HT release results in the activation of multiple 5-HT receptor subtypes. In mice, some receptor subtypes increase PPI when activated, such as the 5-HT_{1A} receptor (Dulawa et al. 1997, 1998), while other subtypes decrease or have no effect on PPI when activated. Presumably, the activation of multiple 5-HT receptor subtypes subsequent to 5-HT release has a cumulative effect on PPI levels. Therefore, the lack of a receptor subtype that decreases PPI should result in increases in PPI subsequent to 5-HT release, as observed here. Thus, the present findings that MDMA and MBDB increase PPI in 1BKO, but not WT mice, indicate that the activation of 5-HT_{1B} receptors by 5-HT decreases PPI. These results are consistent with a previous report that the 5-$HT_{1A/1B}$ agonist RU24969 decreases PPI in WT, but not 1BKO mice (Dulawa et al. 1997, 1998). However, releasing

agents are more physiological tools with which to study the consequences of receptor activation than direct agonists, as the former conserve normal dynamic and anatomical relationships between release and receptor activation, while the latter do not. Thus, converging evidence from studies using direct 5-HT_{1B} agonists (Dulawa et al. 1997) and indirect 5-HT agonists in WT and 1BKO mice indicates that the activation of 5-HT_{1B} receptors disrupts PPI.

MDMA induces the release of dopamine in addition to 5-HT. Because similar results were obtained with MDMA and MBDB, the latter of which has little influence on catecholamine release (Johnson et al. 1986), differential effects of dopamine release are unlikely to be responsible for the present effects of these compounds in the two genotypes. Consistent with this idea is the finding that cocaine has no effect on PPI in WT or 1BKO mice (Dulawa and Geyer, unpublished observations). Furthermore, co-administration of GR 127935 and MDMA increased PPI in intact mice (Fig. 3b), suggesting that the 5-HT-releasing properties, rather than the dopamine-releasing properties of MDMA are responsible for the increase in PPI observed in 1BKO mice.

Constitutive knockout manipulations or the targeted mutation of a gene on day zero can complicate the study of gene function, because compensatory changes may occur during development. Constitutive 1BKO mice have been reported to have compensatory changes in the dopaminergic and serotonergic systems. For example, a 15% increase in dopamine transporter binding in the dorsolateral striatum, a 20% increase in D1 receptor binding in the anterior ventrolateral striatum, a 20% decrease in 5-HT transporter binding, and an increase in D1 receptor mRNA in whole striatum have been found in 1BKO mice (Scearce et al. 1997). Some studies of phenotypic differences between WT and 1BKO mice have mimicked the 1BKO phenotype by administering the 5-$HT_{1B/1D}$ antagonist GR 127935 to intact mice, suggesting that a lack of the 5-HT_{1B} receptor produced the 1BKO phenotype. Other studies using this strategy have not been able to mimic other 1BKO phenotypes, suggesting that developmental changes are responsible for those phenotypes. For example, both 1BKO mice and GR 127935-treated mice show reduced c-Fos induction in the striatum (Lucas et al. 1997; Rocha et al. 1998) and an attenuated locomotor response to MDMA (Scearce-Levie et al. 1999). However, the cocaine-induced increases in locomotion and self-administration observed in 1BKO mice are not reproduced by antagonist treatment in normal mice (Scearce-Levie et al. 1998). The increases in PPI induced by MDMA and MBDB in 1BKO mice in the present experiments were likely due to a lack of the 5-HT_{1B} receptor, and not to altered development, because the 5-$HT_{1B/1D}$ antagonist GR 127935 increased PPI in MDMA-treated intact mice (Fig. 3b).

The PPI-increasing effects of MDMA and MBDB in the 1BKO mice were independent of their effects on startle magnitude. For example, 10 mg/kg MDMA reduced startle magnitude and increased PPI in 1BKO mice, but only at the 6-dB prepulse intensity (Fig. 1). Treatment with 10 mg/kg MBDB increased PPI across all prepulse intensities in 1BKO mice, but had no effect on startle magnitude in either genotype (Fig. 2). Because MDMA, but not MBDB, decreased startle magnitude in the 1BKO mice, dopamine release may have contributed to the decrease in startle observed in experiment 1. As observed in the present studies, we have previously reported that there is no effect of 10 mg/kg MDMA on startle magnitude in intact 129Sv mice (Dulawa and Geyer 1998). Finally, the PPI-increasing effects of MDMA in GR 127935-treated intact mice occurred in the absence of any effect of GR 127935 (0.75, 1.5, and 3.0 mg/kg) on startle magnitude.

The PPI-reducing effect of 5-HT_{1B} receptor stimulation will be possible to localize in the near future. Current information about the neural circuitry modulating PPI suggests that postsynaptic 5-HT_{1B} receptors on striatal GABAergic terminals are responsible for mediating this effect. Previous work in rats suggests that disinhibition or excitation of the ventral pallidum (Swerdlow et al. 1990; Sipes and Geyer 1997) or the facilitation of brain dopaminergic activity (Mansbach et al. 1988; Swerdlow et al. 1991) disrupts PPI. Therefore, the activation of postsynaptic 5-HT_{1B} receptors on striatal GABAergic terminals, which are localized most densely in the ventral pallidum and the VTA/SN, should reduce GABAergic inhibition of ventral pallidal and VTA/SN neurons, causing PPI disruption. 5-HT_{1B} striatal rescue mice, which express 5-HT_{1B} receptors predominantly on striatal GABAergic terminals, will soon be available to test this hypothesis (Stark et al. 1998).

In summary, the 5-HT-releasing compounds MDMA and MBDB increase PPI in 1BKO but not WT mice, indicating that the activation of 5-HT_{1B} receptors decreases PPI. The increased PPI levels observed in 1BKO mice most likely result from a lack of the 5-HT_{1B} receptor, rather than from altered development. Future experiments will examine the role of specific populations of the 5-HT_{1B} receptor in modulating PPI using tissue-specific rescue technology in mice.

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