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ROLIPRAM: A SPECIFIC PHOSPHODIESTERASE 4 INHIBITOR WITH POTENTIAL ANTIPSYCHOTIC ACTIVITY

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Abstract

Currently available antipsychotic medications work primarily by antagonizing D₂ dopamine receptors, thus raising intracellular cAMP levels. We hypothesized that intracellular stimulation of cAMP levels in the CNS would have similar effects to treatment with antipsychotic medication. To test this hypothesis, we studied the effect of an acute treatment of rolipram, an inhibitor of type 4 phosphodiesterases that degrade cAMP, on acoustic startle and prepulse inhibition (PPI) of the acoustic startle response in C57BL/6J mice known to exhibit poor PPI. PPI is disrupted in schizophrenia patients, and the ability of a drug to increase PPI in mice is predictive of antipsychotic efficacy. We show here that acute treatment with rolipram significantly increases PPI at doses that do not alter the acoustic startle response (lowest effective dose 0.66 mg/kg). In addition, rolipram (0.66 mg/kg) blocks the disruptive effects of amphetamine (10 mg/kg) on PPI. At a slightly higher dose (1.0 mg/kg), rolipram also induces catalepsy. Thus, phosphodiesterase-4 (PDE₄) inhibition has many of the same behavioral effects as traditional antipsychotic medications. In contrast to traditional antipsychotics, these effects are achieved through alteration of an intracellular second messenger system rather than antagonism of neurotransmitter receptors. Given previous reports showing rolipram improves cognition, we conclude that PDE₄ represents an important novel target for further antipsychotic drug development.

Keywords

prepulse inhibition; schizophrenia; animal model; psychopharmacology; novel targets; phosphodiesterase inhibitor

Antipsychotic medications are defined by their ability to improve positive symptoms of schizophrenia such as delusions, hallucinations, and disorganized thinking. There are two main classes of antipsychotics: the first-generation medications (e.g. chlorpromazine and haloperidol), and the newer, atypical antipsychotics, (e.g. clozapine, risperidone and olanzapine) (Miyamoto et al., 2005). Regardless of class, antipsychotic potency is proportional to blockade at dopamine D₂ receptors (Kanes et al., 1993; Kapur and Seeman, 2001; Seeman, 2002; Kapur and Mamo, 2003), which are tonically active (Adell and

Artigas, 2004). Because of D₂ blockade, patients are at high risk of developing extrapyramidal side effects (EPS) and hyperprolactinemia. By varying potency at other neurotransmitter receptors including the 5-HT_{2a} receptor, newer medications are less likely to cause EPS, but are more likely to cause cardiac conduction abnormalities, sedation, and weight gain (Serretti et al., 2004). Although not part of the formal diagnostic criteria, schizophrenia is also associated with neurocognitive and neurophysiologic dysfunctions including problems with learning and memory, executive function, sensorimotor gating, eye tracking and olfaction (Censits et al., 1997; Gur et al., 2001, 2003; Hill et al., 2002; Lowery et al., 2003; Sachs et al., 2004). Current treatments are more effective at treating the positive symptoms of schizophrenia than the negative or neurophysiologic symptoms. Although they can measurably improve some neurocognitive (Keefe et al., 2004) and neurophysiologic abnormalities (Gonul et al., 2003), others remain untouched (e.g. Sumiyoshi et al., 2003). Thus, the ability of currently available antipsychotics to improve daily functioning and productivity is questionable (Duncan et al., 2003a,b; Percudani et al., 2004), particularly when both antipsychotics and D₂-antagonists have actually been shown to impair learning in several rodent models (Ploeger et al., 1992, 1994; Setlow and McGaugh, 1998; Greba et al., 2001; Rosengarten and Quartermain, 2002). Therefore, there is a need to develop novel medications to treat schizophrenia that will control all symptoms while eliminating many of the side effects associated with current medications (Meltzer, 2003).

Currently available antipsychotics block D₂ receptors (Kehne et al., 1991; Kapur and Mamo, 2003), resulting in increased cAMP levels in the brain (e.g. Kelly et al., 2006). As such, we explored the possibility that increasing cAMP levels via intracellular targets might provide a novel therapeutic avenue in the development of antipsychotics. One potential target is the phosphodiesterase-4 (PDE₄) family of enzymes, one of 11 families of enzymes that degrade cyclic nucleotides (c.f., Beavo and Brunton, 2002; Lugnier, 2006). The PDE₄ family has several isoforms that are widely distributed in the brain and specifically catalyze the hydrolysis of cAMP. Interestingly, a compensatory increase in cAMP PDE activity has been observed in an endophenotypic mouse model of schizophrenia (Kelly et al., 2006). Further, a physical interaction between disrupted in schizophrenia 1 (*DISC1*) and PDE_{4B}, along with cytogenetic alterations in PDE_{4B} in human patients with schizophrenia, has been observed (Millar et al., 2005). Inhibition of PDE₄ is likely to result in selective physiological effects because PDE₄ is compartmentalized to microdomains via binding partners, such as β -arrestins and A-kinase anchoring proteins (Houslay and Adams, 2003; Mongillo et al., 2004; Dodge-Kafka et al., 2005). As such, PDE₄ regulates cAMP-stimulated crosstalk between specifically complexed proteins, such as protein kinase A and β -adrenergic receptors (Perry et al., 2002; Baillie et al., 2003). Importantly, PDE₄ inhibitors are likely to be clinically available in the near future as they are currently in phase II clinical trials (Houslay et al., 2005).

Rolipram, a potent inhibitor of PDE₄, increases both the intensity and duration of cAMP-mediated signaling (Scuvee-Moreau et al., 1987). Rolipram has a number of important psychoactive properties including acting like an antidepressant (Bonbon et al., 1988), reducing morphine-induced hyperlocomotion (Mori et al., 2000), and enhancing hippocampus-dependent memory and LTP (Randt et al., 1982; Barad et al., 1998; Bourchouladze et al., 2003). In addition, rolipram blocks the development of haloperidol-induced vacuous chewing movement (Sasaki et al., 1995), a standard behavioral screen for the development and treatment of tardive dyskinesia. Because of the possibility of aberrant cAMP signaling in schizophrenia, the potential of improving learning and memory functioning, and the likelihood of preventing or treating tardive dyskinesia, we studied the effect of rolipram in several behavioral paradigms with strong predictive validity for antipsychotic activity.

To assess the potential antipsychotic activity of rolipram, we tested the effect of this drug in a paradigm of sensorimotor gating referred to as prepulse inhibition of acoustic startle (PPI). We chose this paradigm not only because patients with schizophrenia exhibit PPI deficits (Braff et al., 1978), but also because the ability of a drug to increase PPI in rodents predicts the clinical efficacy of antipsychotic medications (Swerdlow et al., 1998; Geyer et al., 2001). PPI is a behavioral paradigm in which the presentation of a non-startling stimulus (prepulse, e.g. 72 dB noise) inhibits the startle response elicited by a subsequently presented startling acoustic stimulus (e.g. 120 dB noise). Here, we tested the dose-dependent ability of rolipram to increase baseline PPI in C57BL/6J mice. C57BL/6J mice exhibit poor PPI relative to other strains (Paylor and Crawley, 1997; Dulawa and Geyer, 2000; Ouagazzal et al., 2001) and, as such, have been proposed as a predictive model for testing of antipsychotic efficacy (Ouagazzal et al., 2001). In addition, we tested the ability of rolipram to reverse amphetamine-induced disruption of PPI as well as the dose-dependent ability of rolipram to induce catalepsy, the latter of which evaluates the potential for causing EPSs. Given the ability of rolipram to improve memory, an antipsychotic-like profile in these behavioral paradigms could lead to the development of improved therapeutics that are capable of resolving the positive symptoms and the debilitating cognitive deficits experienced by patients with schizophrenia.

EXPERIMENTAL PROCEDURES

Mice

Eight to 10 week old male C57BL/6J mice were purchased from Jackson Laboratory (Bar Harbor, ME, USA). Mice were housed in an Association for Assessment of Accreditation of Laboratory Animal Care–approved animal facility at the University of Pennsylvania. Mice were maintained on a 12-h light/dark cycle and housed in a light- and temperature-controlled facility with food and water available *ad libitum*. Behavioral testing was performed during the light phase. Mice were acclimated to the housing facility for 1–2 weeks prior to behavioral testing. All protocols were approved by the Institutional Animal Care and Use Committee and were conducted in accordance with and National Institutes of Health guidelines. Every effort was made to reduce suffering experienced by the subjects and the number of mice used.

Startle response and prepulse inhibition tests

Startle responses to acoustic stimuli and inhibition of startle responses due to presentation of a non-startling prepulse were initially measured, as previously described (protocol 2; Gould et al., 2004; Kelly et al., 2006). Startle responses were measured by an accelerometer in response to acoustic stimuli delivered by a white noise generator (4–19 kHz) (SR-Laboratory; San Diego, CA, USA). Testing was conducted in one of two facilities, one in which the background (bg) noise played in the chamber was set to 65 dB and the other in which the bg was set to 68 dB. There was no difference between datasets; therefore, all data collected in the two facilities were combined for subsequent analyses (see *Data Analysis* below). Sessions began with a 5 min block of acclimation to the bg noise, followed by a block of five 120 dB startle pulses in an effort to make subsequently measured startle responses less variable. During the next 10 min block, startle responses were measured to 40 ms pulses of 0, 90, 95, 100, 105, 110, 115 and 120 dB, presented each five times in a random order with an intertrial interval randomized from 10 to 20 s. The startle portion of the session concluded with an additional block of five 120 dB pulses to assess potential effects on habituation. Startle trials were followed by a 10 min block of PPI trials. Each prepulse trial consisted of a 20 ms prepulse 4, 8, or 16 dB above bg, followed 100 ms later by a 40 ms pulse of 120 dB. Five trials of each prepulse intensity along with 10 startle-only trials (i.e. trials with no prepulse) were presented in random order. Startle responses were

collected as 60, 1 ms voltage readings, which were averaged over the collection interval to give an average measure for each trial (Gould et al., 2004).

Startle responses and inhibition of startle responses were also measured in pilot studies based on “Protocol 1” of Gould and colleagues (2004). This protocol is similar to that described above, with a 65 dB bg noise, except that the startle portion of the session also includes trials at 125 dB. Further, PPI trials consisted of 75, 80, 85, 90, and 95 dB prepulses with a 40 ms interstimulus interval between the prepulse and 120 dB startle stimulus. Finally, data were recorded as 100 1 ms voltage readings, which were averaged over the collection interval to give an average startle measure for each trial. These data are not shown, but rolipram yielded similar dose-response and amphetamine-reversal effects using this protocol.

PPI for a given prepulse intensity was calculated as percent inhibition of the startle response using the following formula: $[100 - (\text{average startle response for PPI trials} / \text{average startle response for startle-only trials in PPI block}) \times 100]$.

Catalepsy testing

Catalepsy testing was performed as previously described (Kanes et al., 1993, 1996). Mice were removed from their home cage to a testing cage 1 h prior to testing. Fifteen minutes after injection mice were positioned in a fixed rearing posture in the test cage. Mice were rated by two independent raters as cataleptic if they maintained this posture for 300 s or longer. Release from catalepsy was scored if one or more forepaws touched the floor of the test cage.

Drugs

Rolipram and D-amphetamine sulfate were purchased from Sigma Inc. (St. Louis, MO, USA). For behavioral testing D-amphetamine was dissolved in 0.9% sterile saline, rolipram was dissolved in 2% (v/v) DMSO/0.9% saline. Rolipram was administered 15 min prior to the behavioral session at doses of 0.1–10.0 mg/kg (as indicated), with animals remaining in a holding cage during the injection-session interim. The doses of rolipram selected (0.1–10 mg/kg) have been previously tested in paradigms of both learning and memory (Barad et al., 1998) and acoustic startle (Kehne et al., 1991) and have been shown to increase cAMP levels in the absence of neuronal stimulation (Gold et al., 2002).

D-Amphetamine was administered immediately prior to the behavioral session at a dose of 10 mg/kg, as this has previously been shown to impair PPI in C57BL/6 mice (Ralph-Williams et al., 2003). Haloperidol (Ben Venue Laboratories Inc., Bedford, OH, USA) was dissolved in saline with lactic acid, pH 3.0–3.8 (0.01 or 0.1 mg/ml) and administered at a dose of 0.1 mg/kg or 1.0 mg/kg, based on our previous work in transgenic mice (Kelly et al., 2006). All injections were given i.p. at a volume of 1.0 ml/kg body weight.

Data analysis

For the rolipram experiments, data from the PPI trials were not normally distributed *across* trials. As such, data could not be analyzed across trials using a parametric approach (repeated measures analysis of variance (ANOVA)). These data were, however, normally distributed *within* trials. Thus, data from each trial were analyzed using ANOVA, with the Student-Newman-Keuls (SNK) post hoc approach used to accommodate multiple testing (Sigmastat 2.03; Sigmastat, San Jose, CA, USA). The outcomes from the startle trials were not generally normally distributed within trials. Therefore, a nonparametric alternative to the ANOVA, the Kruskal-Wallis test was used in place of the ANOVA, with post hoc testing performed using Dunn’s approach (Sigmastat 2.03). For the haloperidol experiments, the

variables were normally distributed both within and across PPI trials. Thus, data for these experiments were analyzed by a repeated measures ANOVA (for effects of treatment and trial), with post hoc testing by SNK. Data for startle trials were normally distributed within trials (but not across trials), thus, each trial was analyzed separately ANOVA with post hoc by SNK. For both rolipram and haloperidol experiments, habituation of the startle response was calculated as a difference score (average startle response to the block of 120 dB trials before the randomized startle trials minus the average startle response to the block of 120 dB trials that followed the randomized startle trials). Habituation data were normally distributed and analyzed by ANOVA with post hoc by SNK. In addition, Pearson product moment correlations were conducted to determine if there was an interrelation between startle magnitude (during 120 dB pulse-only trials of the PPI section, which were normally distributed) and % PPI, as previously described (Quednow et al., 2006; Kelly et al., 2006). Catalepsy data were analyzed by χ^2 analysis using Prism 4 software (GraphPad Inc., San Diego, CA, USA). Statistical significance was determined at $P \leq 0.05$.

RESULTS

Rolipram increases PPI in a dose-dependent manner

We tested directly the hypothesis that increasing cAMP levels would increase PPI (based on “Protocol 2,” Gould et al., 2004; Kelly et al., 2006). Using C57BL/6J mice, we examined the effect of vehicle vs. four doses of rolipram (0.1, 0.66, 1 and 10 mg/kg), a PDE₄ inhibitor known to increase cAMP levels ($n = 18$ per group; Fig. 1). Rolipram increased PPI at select prepulse intensities. In trials where the prepulse was played 8 dB above bg, rolipram significantly increased PPI in a dose-dependent manner ($F_{(4,85)} = 13.67$, $P < 0.001$). Post hoc analyses revealed that 0.66 mg/kg and 1.0 mg/kg rolipram increased PPI relative to both vehicle ($P = 0.022$ and $P < 0.001$, respectively) and 0.1 mg/kg rolipram ($P = 0.008$ and $P < 0.001$, respectively), and 10 mg/kg rolipram increased PPI relative to vehicle ($P < 0.001$), 0.1 mg/kg ($P < 0.001$) and 0.66 mg/kg rolipram ($P = 0.007$). Rolipram also increased PPI in a dose-dependent manner when the prepulse was played 16 dB above bg ($F_{(4,85)} = 36.11$, $P < 0.001$). Post hoc analysis revealed that 0.66 mg/kg significantly increased PPI relative to vehicle and 0.1 mg/kg rolipram ($P < 0.001$ for each), 1.0 mg/kg increased PPI relative to vehicle ($P < 0.001$), 0.1 mg/kg ($P < 0.001$), and 0.66 mg/kg rolipram ($P = 0.009$), and 10 mg/kg increased PPI relative to vehicle ($P < 0.001$), 0.1 mg/kg ($P < 0.001$), 0.66 mg/kg ($P < 0.001$), and 1.0 mg/kg rolipram ($P = 0.015$). Importantly, rolipram did not affect the startle response itself in pulse-only trials (120 dB) during the PPI portion of the session.

Rolipram alters acoustic startle response in a stimulus dependent manner

Previous studies in rats indicated that rolipram can increase acoustic startle, depending on the site of administration (Kehne et al., 1991); therefore, we tested the ability of rolipram to alter the startle response in mice. In the present study rolipram generally decreased the acoustic startle response in C57BL/6J mice (Fig. 2). In the “no stimulation” trial, there was a significant effect of rolipram ($H_{(4)} = 11.98$, $P = 0.017$), with post hoc testing showing that 10 mg/kg reduced responses relative to vehicle. In the 90 dB trial, there was also an effect of rolipram ($H_{(4)} = 10.00$, $P = 0.04$); however, no post hoc comparisons reached the level of significance. Similar to the “no stimulation” trial, there was a significant effect of rolipram at 95 dB ($H_{(4)} = 16.01$, $P < 0.003$), with post hoc testing showing that 10 mg/kg significantly suppressed responses relative to vehicle. In the 100 dB ($H_{(4)} = 30.20$, $P < 0.001$) and 105 dB trials ($H_{(4)} = 18.12$, $P = 0.001$), there was even a greater effect of rolipram on startle, with post hoc testing revealing a significant suppressing effect of 0.66 mg/kg, 1.0 mg/kg, and 10 mg/kg rolipram in the former and of 0.66 mg/kg and 10 mg/kg in the latter. No significant effect of rolipram was detected in the 110 dB, 115 dB, or the 120 dB trials. Importantly, there were no significant correlations between startle magnitude in the pulse-only trials (120

dB) and % PPI for any trial in any group, suggesting that the augmentation of PPI noted above was not due to the non-significant effect of rolipram on startle. Finally, there was no significant effect of rolipram on habituation.

Rolipram increases PPI at doses similar to haloperidol

To determine the relative efficacies of rolipram vs. haloperidol in increasing PPI, we next determined at which dose haloperidol increases PPI in C57BL/6J mice using our protocol. To do so, we compared the effect of 0.1 mg/kg and 1.0 mg/kg haloperidol relative to vehicle ($n = 8$ per group; Fig. 3). Across prepulse intensities, there was a significant effect of treatment ($F_{(2,42)} = 3.64$, $P = 0.044$). Post hoc tests showed that 1.0 mg/kg haloperidol significantly improved PPI across prepulse intensities relative to vehicle treatment ($P = 0.037$).

During the startle portion of the session, haloperidol significantly affected responses during the “no stimulation” trial ($F_{(2,21)} = 5.08$, $P = 0.016$), with post hoc tests showing that both 0.1 mg/kg (3.69 ± 0.4 units) and 1.0 mg/kg haloperidol (3.11 ± 0.3 units) significantly reduced movement relative to vehicle (5.05 ± 0.6 units, $P = 0.041$ and $P = 0.014$, respectively). Despite this effect, there was no effect of haloperidol in startle trials ranging from 90 dB to 120 dB. Further, there was no effect of haloperidol on habituation. Finally, mice treated with 1.0 mg/kg haloperidol showed no correlations between startle magnitude of pulse-only trials and % PPI in any trial, suggesting that the ability of haloperidol to increase PPI is not due to a non-significant change in startle.

Rolipram ameliorates disruption of PPI by D -amphetamine

Given that rolipram was able to increase baseline PPI, we next tested the ability of 0.66 mg/kg rolipram to block disruption of PPI by D -amphetamine ($n = 14$ for each group; Fig. 4). D -Amphetamine is a psychotomimetic known to disrupt PPI, and the ability of an antipsychotic to reverse this disruption strongly predicts clinical efficacy (Swerdlow et al., 1998; Geyer et al., 2001). As previously shown in C57BL/6J mice, D -amphetamine impaired PPI at all prepulse intensities (4 above bg, $F_{(1,52)} = 4.04$, $P = 0.05$; 8 above bg, $F_{(1,52)} = 5.01$, $P = 0.03$; 16 above bg, $F_{(1,52)} = 6.78$, $P = 0.012$). Despite a disruptive effect of D -amphetamine, pretreatment with 0.66 mg/kg rolipram significantly increased PPI in trials with prepulses 8 dB ($F_{(1,52)} = 4.65$, $P = 0.036$) and 16 dB above bg ($F_{(1,52)} = 5.08$, $P = 0.028$) and showed a trend toward increasing PPI in trials with prepulses 4 dB above bg ($F_{(1,52)} = 2.95$, $P = 0.092$). Post hoc analyses for the 4 dB trial revealed no significant effects; however, the 8 dB and 16 dB PPI trials showed that rolipram only increased PPI in amphetamine-treated animals (veh-veh vs. veh-amph, $P = 0.032$ and $P = 0.022$; veh-amph vs. rol-amph, $P = 0.037$ and $P = 0.038$; veh-veh vs. rol-veh, $P = \text{NS}$; rol-veh vs. rol-amph, $p = \text{NS}$).

Rolipram does not reverse the effects of amphetamine on acoustic startle

Amphetamine causes a dose-related impairment in acoustic startle response in mice (Ralph-Williams et al., 2002) that is not reversed by antipsychotic medication. In general, treatment with either D -amphetamine (10 mg/kg), rolipram (0.66 mg/kg), or both reduced startle responses of C57BL/6J mice across dB intensities; however, this effect only reached the level of statistical significance in select trials (Fig. 5). In the “no stimulation” trial, there was a significant effect of treatment ($H_{(3)} = 25.98$, $P < 0.001$), with post hoc analyses showing that both groups of animals treated with amphetamine exhibited an increased response. There was also a significant effect of treatment in the 90 dB and 95 dB trials ($H_{(3)} = 10.26$, $P = 0.016$ and $H_{(3)} = 10.01$, $P = 0.019$, respectively), with post hoc analyses revealing rol-veh-treated mice showed significantly reduced responses only relative to veh-amph mice. For 100–120 dB trials, there was no significant effect of treatment. There was, however, a

significant effect of treatment on habituation of the startle response ($F_{(3,52)} = 4.11$, $P = 0.011$). Post hoc analyses showed that veh-amph-treated mice failed to demonstrate appreciable habituation (-8.53 ± 8.4 units; veh-amph vs. veh-veh, rol-veh, and rolamph, $P = 0.014$ – 0.023). Rolipram pretreatment blocked amphetamine-disruption of habituation as rol-amph-treated mice showed levels of habituation (28.87 ± 12.2 units) that did not significantly differ relative to veh-veh (38.09 ± 12.7 units) or rol-veh-treated mice (40.99 ± 11.3 units).

Rolipram induces catalepsy

The ability of a drug to cause catalepsy, is predictive of both its potential for antipsychotic efficacy as well as its liability to cause EPSs (Hoffman and Donovan, 1995). Rolipram was compared with haloperidol, a canonical antipsychotic that works through D_2 dopamine receptor blockade (Table 1). Rolipram induced catalepsy at doses lower than those of haloperidol ($\chi^2_{(2)} = 7.85$, $P < 0.05$). The lowest dose of rolipram that caused catalepsy was 1.0 mg/kg, whereas the lowest dose for haloperidol was 5.0 mg/kg (Table 1); 0.66 mg/kg did not cause appreciable catalepsy.

DISCUSSION

By measuring PPI in C57BL/6J mice we have examined the potential antipsychotic activity of rolipram. Rolipram is a drug that increases cAMP levels by inhibiting PDE_4 , an enzyme that degrades cAMP. Our results show that rolipram increases baseline PPI in a dose-dependent manner and blocks the disruption of PPI caused by amphetamine. These effects of rolipram on PPI are elicited at marginally sub-cataleptic doses. These data support previous studies in endophenotypic mouse models of schizophrenia, in which rolipram rescued pharmacological disruption of sensory gating (Maxwell et al., 2004) and latent inhibition (Davis and Gould, 2005) as well as genetic disruption of PPI (Kelly et al., 2006).

The ability of a compound to increase baseline PPI in mice has been proposed as a valid pharmacologic screen for antipsychotic efficacy (Ouagazzal et al., 2001). C57BL/6J, BALB/cBYJ, MORO, 129/SvEv mice all exhibit significant increases in baseline PPI after administration of haloperidol, clozapine and risperidone. We found that rolipram increases baseline PPI in mice at doses (0.66–10 mg/kg) that may possibly be clinically meaningful. A preliminary open-label trial of rolipram in the treatment of schizophrenia, 0.64 mg/kg (45 mg/day) was effective in reducing Brief Psychiatric Rating Scale scores during the first week of treatment (Pietzcker et al., 1979). It should be noted, however, that it is problematic to compare effective doses for behavioral effects of rolipram between species due to differences in bioavailability (Krause and Kuhne, 1988). We can, however, compare doses used in the current experiments with others used in mice. The effective doses found in the current study (0.66–10 mg/kg) are similar to those shown to elicit anti-depressant (0.5 mg/kg/day; Zhang et al., 2002; Li et al., 2003) and anti-inflammatory effects in mice (6.25 mg/kg/day; Sommer et al., 1997), but are substantially higher than those shown to reverse memory deficits in mice (0.1 mg/kg; Zhang et al., 2000, 2004; Bourtchouladze et al., 2003). Further, the minimal dose of rolipram shown to increase PPI here (0.66 mg/kg) was similar that for haloperidol (1.0 mg/kg).

In addition to improving baseline PPI, rolipram ameliorates amphetamine-induced disruption of PPI and habituation of the acoustic startle response. Although we cannot strictly rule out the possibility that the ability of rolipram to rescue amphetamine-induced disruptions in PPI simply reflects the ability of rolipram to increase baseline PPI, we believe several facts argue against this scenario. First, in this experiment (which employed two injections) rolipram only increased PPI in amphetamine-treated not vehicle-treated mice. Further, the difference in % PPI between veh-amph- and rol-amph-treated mice (8 dB above bg, 18%; 16 dB above bg, 16%) is twice that between veh-veh- and rol-veh-treated mice (8

dB above bg, 7%; 16 dB above bg, 8%). Finally, rolipram did not significantly affect baseline habituation of the startle response. It is also worth noting, that the ability of a drug to increase baseline PPI does not necessarily correspond to an ability to increase amphetamine-disrupted PPI (e.g. Brody et al., 2003; Ong et al., 2005). Taken together, we believe these data suggest that the ability of rolipram to rescue amphetamine-induced disruptions does not simply reflect a shifted baseline.

Amphetamine is a widely used pharmacologic model that attempts to mimic the disruption in PPI seen in patients with schizophrenia. The ability of amphetamine to disrupt PPI requires D₂ receptors (Ralph et al., 1999; Ralph-Williams et al., 2002; but see Ralph-Williams et al., 2003) that inhibit cAMP production (Neves et al., 2002). Interestingly, the dose of amphetamine used here (10 mg/kg) increases cAMP levels in striatum but decreases cAMP levels in cortex of C57BL/6J mice (Kelly et al., 2006). It is likely that it is this reduction in cortical cAMP signaling that primarily mediates amphetamine-disruption of PPI because decreasing cAMP signaling in the brain of C57BL/6J mice is sufficient to induce PPI deficits (Kelly et al., 2006). The ability of rolipram to rescue amphetamine-induced deficits in PPI further suggests that it is the decreases in cortical cAMP—and not the increases in striatal cAMP—that mediate the effect of amphetamine on PPI. We believe this is further support for the hypothesis that PPI in C57BL/6J mice is not only regulated by a complex neural circuitry, but also a molecular signature that exhibits regional specificity (Kelly et al., 2006).

The ability of a compound to induce catalepsy is a measure of striatal dopamine receptor blockade (Wadenberg et al., 2000). This is predictive of both antipsychotic efficacy as well as a compound's propensity to induce EPSs. Our results show that rolipram induces catalepsy with a potency similar to that of haloperidol, suggesting an antipsychotic-like effect. Although the lowest effective dose of rolipram to increase PPI (0.66 mg/kg) did not induce catalepsy, a dose only slightly higher did (1.0 mg/kg). Despite this ability to induce catalepsy, it should be noted that rolipram reduces vacuous chewing movements due to chronic haloperidol treatment (Sasaki et al., 1995).

The results presented here indicate that rolipram, a prototypical PDE₄ inhibitor, may act as an effective antipsychotic. It will be of interest to future studies to determine if rolipram is capable of reversing amphetamine-induced hyperlocomotion or glutamatergic disruption of PPI, given that rolipram rescues glutamatergic disruption in tasks related to memory (Zhang et al., 2000) and latent inhibition (Davis and Gould, 2005). Although rolipram itself may be limited in its clinical utility by emetic and sedative side effects, there are newer compounds in development that appear to have reduced side effects, possibly due to a greater PDE₄-subtype selectivity (Houslay et al., 2005). Our findings, combined with previous indications of improved learning and memory, mood, and, potentially, tardive dyskinesia, indicate that PDE₄ inhibition represents a new frontier in antipsychotic development. Inhibition of intracellular second messenger cascades may provide the path to new and more effective treatments for patients with severe symptoms.

Abbreviations

ANOVA	analysis of variance
bg	background
EPS	extrapyramidal side effects
PDE	phosphodiesterase
PPI	prepulse inhibition of acoustic startle

SNK

Student-Newman-Keuls

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Fig. 1.

Rolipram increases PPI in a dose-dependent manner. Rolipram (rol), administered 15 min before testing, produced a dose-dependent increase in PPI. Overall, 10 mg/kg rolipram had the greatest effect at all prepulse intensities, with significant increases also observed for doses of 0.66 mg/kg and 1 mg/kg. In addition, the largest effects of rolipram were seen at higher prepulse intensities. $n=18$ per group. Post hoc [@] vs. vehicle and 0.1 mg/kg, $P<0.025-0.001$; [#] vs. vehicle, 0.1 and 0.66 mg/kg, $P<0.01-0.001$; [^] vs. vehicle, 0.1, 0.66, and 1 mg/kg, $P<0.02-0.001$.

Fig. 2.

Rolipram decreases startle magnitude to lower intensity stimuli only. Rolipram generally decreased startle responding at doses of 0.66 mg/kg to 10 mg/kg. Importantly, there was no effect of rolipram in response to a 120 dB stimulus, the intensity used in PPI trials; $n=18$ mice per treatment group. Post hoc * vs. vehicle, $P<0.05$.

Fig. 3. Haloperidol (hal) increases PPI in a dose-dependent manner. Across prepulse intensities, 1.0 mg/kg hal, but not 0.1 mg/kg hal significantly increased PPI relative to vehicle; $n=8$ per group. Post hoc for effect of treatment across trials, * vs. vehicle, $P<0.05$.

Fig. 4.

Rolipram (rol) ameliorates the impairment in PPI caused by amphetamine. Relative to vehicle, D-amphetamine (10 mg/kg; amph) disrupted PPI; however, pretreatment with rol (0.66 mg/kg) blocked this disruption; $n=14$ per group. ^ Main effect of amphetamine, $P=0.05$; post hoc * vs. veh-veh, $P<0.05$; @ vs. veh-amph, $P<0.05$.

Fig. 5.

Rolipram (rol) neither augments nor reverses the effects of amphetamine on startle responses to higher intensity stimuli. D-Amphetamine (10 mg/kg; amph) generally reduced acoustic startle responses to higher intensity stimuli (105 dB and greater), but not to the level of statistical significance. As above, rol (0.66 mg/kg) reduced acoustic startle responses. There was neither a rescue nor an additive effect of rol plus amphetamine on startle responses to higher intensity stimuli; however, amphetamine appeared to block the ability of rol to reduce startle responses to lower intensity stimuli; $n=14$ mice per treatment group. Post hoc * vs. veh-veh, $P<0.05$; @ vs. veh-amph, $P<0.05$; # vs. veh-amph and rol-amph, $P<0.05$.

Table 1

Dose response for catalepsy induced by rolipram and haloperidol

Dose (mg/kg, i.p)	Percent cataleptic
Rolipram	
0.0 (Vehicle)	0 (8)
0.1	0 (10)
0.66	0 (10)
1.0	13 (8)
5.0	46 (10)
10.0	100 (8)
Haloperidol	
0.0 (Vehicle)	0 (8)
0.1	0 (8)
0.66	0 (8)
1.0	0 (10)
5.0	10 (10)
10.0	80 (10)

Both rolipram and haloperidol induced catalepsy 15 min after drug administration in a dose-dependent fashion. The size of each group is shown in parentheses.