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ORIGINAL INVESTIGATION

Dissociable effects of the $_{d}$- and $_{l}$- enantiomers of govadine on the disruption of prepulse inhibition by MK-801 and apomorphine in male Long-Evans rats

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Abstract
Rationale The search for novel antipsychotic drugs to treat schizophrenia is driven by the poor treatment efficacy, serious side effects, and poor patient compliance of current medications. Recently, a class of compounds known as tetrahydroprotoberberines, which includes the compound $_{d,l}$-govadine, have shown promise in preclinical rodent tests relevant to schizophrenia. To date, the effect of govadine on prepulse inhibition (PPI), a test for sensorimotor gating commonly used to assess the effects of putative treatments for schizophrenia, has not been determined.
Objectives The objective of the present study was to determine the effects of each enantiomer of govadine ($_{d}$- and $_{l}$-govadine) on PPI alone and its disruption by the distinct pharmacological compounds apomorphine and MK-801.
Methods Male Long-Evans rats were treated systemically with $_{d}$- or $_{l}$-govadine and apomorphine or MK-801 prior to PPI. The PPI paradigm employed here included parametric manipulations of the prepulse intensity and the interval between the prepulse and pulse.
Results Acute MK-801 (0.15 mg/kg) significantly increased the startle response to startle pulses alone, while both MK-801 and apomorphine (0.2 mg/kg) significantly increased reactivity to prepulse-alone trials. Both MK-801 and apomorphine disrupted PPI. In addition, $_{d}$-govadine alone significantly disrupted PPI in the apomorphine experiment. Pretreatment with $_{l}$-, but not $_{d}$-, govadine (1.0 mg/kg) blocked the effect of apomorphine and MK-801 on PPI. Treatment of rats with $_{l}$-govadine alone (0.3, 1.0, 3.0 mg/kg) also dose-dependently increased PPI.
Conclusions Given the high affinity of $_{l}$-govadine for dopamine D2 receptors, these results suggest that further testing of $_{l}$-govadine as an antipsychotic is warranted.

Keywords Dopamine · Antipsychotic · Schizophrenia

Introduction

Schizophrenia is a debilitating psychiatric disorder that affects approximately 1% of the global population. Current treatment options are not effective for all symptoms of the disorder and as a result, novel compounds with potential for use in schizophrenia are currently under development. One family of compounds known as tetrahydroprotoberberines (THPBs), derived from traditional Chinese medicine, have unique dopamine-related activity (Jin et al. 2002; Yang et al. 2007; Natesan et al. 2008; Zhai et al. 2012; Lapish et al. 2012). Govadine is a synthetic THPB that exists as two enantiomers, $_{d}$- and $_{l}$-govadine ($_{d}$-Gov, $_{l}$-Gov), each with distinct pharmacological profiles (Zhai et al. 2012; Lapish et al. 2014). Affinity for D1 and D2S classes of dopamine receptors is comparable between $_{d}$- and $_{l}$-Gov. However, a large difference

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in affinity for the D2L receptor exists between l-Gov (165 nM) and d-Gov (1340 nM). Affinities for other receptor types that are comparable between the two enantiomers are low in relation to these different classes of dopamine receptors (Lapish et al. 2014). Studies using microdialysis determined l-Gov increases dopamine (DA) efflux in both the prefrontal cortex (PFC) and nucleus accumbens (NAc), whereas d-Gov only increases DA efflux in the PFC (Lapish et al. 2014). Previous research using rats suggests govadine may have the unique ability to improve the three major symptom categories seen in schizophrenia: positive, negative, and cognitive (Lapish et al. 2012, 2014). When examined separately, l-Gov, but not d-Gov, blocks amphetamine-induced hyperlocomotion, impairs conditioned avoidance responding, and induces catalepsy similarly to antipsychotic drugs with high affinity for the D2L receptor. In contrast, d-Gov displays primarily pro-cognitive effects by reducing errors on the delayed-spatial win-shift task and improving temporal order memory at a long delay. Both enantiomers successfully reversed social interaction deficits, a measure of negative symptoms, as well as amphetamine-disrupted latent inhibition (Lapish et al. 2014). l-Gov, but not d-Gov, reverses MK-801-induced impairments in a touch-screen visuo-spatial paired associates learning task (Lins et al. 2015). These data encourage further investigation of govadine enantiomers as a putative treatment for schizophrenia.

Prepulse inhibition (PPI) refers to the reduced motor response to a startling stimulus, such as an auditory tone or "pulse," when the startling stimulus is preceded by another low-intensity sensory input in close temporal proximity (Koch and Schnitzler 1997; Geyer et al. 2001a; Yeomans et al. 2006). Therefore, PPI is a common measure of sensorimotor gating used in studies of humans or animals including rodents and has cross-species validity, face validity, ease of implementation, and reliability. The predictive validity of PPI is related to the finding that compounds which reverse drug-induced PPI disruptions in rodents very often have antipsychotic efficacy in humans (Swerdlow et al. 2006, 2016a, b). PPI is commonly measured with auditory pulses and prepulses, although other cross-modal paradigms have been developed. PPI is impaired in several psychiatric illnesses including schizophrenia (Braff et al. 1978; Braff and Geyer 1990; Grillon et al. 1992), obsessive compulsive disorder (Swerdlow et al. 1993), Huntington's disease (Swerdlow et al. 1995), and Tourette's syndrome (Castellanos et al. 1996).

The neural circuitry regulating PPI includes an array of limbic, cortical, striatal, pallidal, and pontine brain areas collectively known as the "CSPP" circuitry (Swerdlow et al. 2001a, 2016a, b). PPI is disrupted following systemic administration of the dopamine agonists apomorphine and amphetamine (Geyer et al. 1987; Mansbach et al. 1988) and non-competitive N-methyl-D-aspartate receptor (NMDAR) antagonists such as MK-801 (dizocilpine) (Mansbach and Geyer 1989, 1991; al-Amin and Schwarzkopf 1996; Bast et al. 2000). The effects of typical and atypical antipsychotic drugs on PPI have been studied extensively. Typical antipsychotics such as haloperidol, a D2 antagonist, effectively reverse deficits in PPI induced by acute pharmacological challenge with apomorphine (Swerdlow and Geyer 1993) but not MK-801 or phencyclidine (Geyer et al. 1990; Keith et al. 1991; Johansson et al. 1994). In contrast, atypical antipsychotics reverse the impairments following either apomorphine or MK-801 treatment, although some inconsistencies have been reported. Apomorphine-induced deficits are blocked by clozapine (Swerdlow and Geyer 1993) whereas clozapine, quetiapine, and olanzapine either improve (Bakshi et al. 1994; Bakshi and Geyer 1995; Swerdlow et al. 1996, 1998; Zhang et al. 1997; Bubenikova et al. 2005) or do not affect acute MK-801-induced impairments in PPI (Bast et al. 2000). Zotepine and risperidone do not restore PPI following MK-801 treatment (Swerdlow et al. 1996; Varty et al. 1999; Bubenikova et al. 2005). Further, PPI disrupted by either MK-801 or PCP is resistant to reversal by specific antagonism of D1, D2, or 5-HT2 receptors (Keith et al. 1991; Bakshi et al. 1994). When administered alone, olanzapine and clozapine also decrease PPI in some studies (Bubenikova et al. 2005) but not others (Depoortere et al. 1997). The distinctions in PPI disruption caused by apomorphine or MK-801 and the different approaches needed to ameliorate them may be relevant to different schizophrenia patient populations, with those compounds that reverse effects of MK-801 having the prospect of antipsychotic efficacy for individuals resistant to current therapies (Al-Amin and Schwarzkopf 1996).

Given the distinct effects of typical and atypical antipsychotic drugs on the disruption of PPI by apomorphine and MK-801, we tested the effects of each enantiomer of govadine on these drug-induced disruptions of PPI. PPI can fluctuate depending on the interaction of drug treatment with specific PPI protocol parameters in both clinical populations and rodents (Ballendine et al. 2015; Chandna et al. 2015; Duncan et al. 2001; Howland et al. 2012; Pinnock et al. 2015; Swerdlow et al. 2016a, b, 2008). Therefore, the PPI protocol employed a range of prepulse-pulse intervals (30, 50, 80, and 140 ms) and prepulse intensities (3, 6, and 12 dB). We hypothesized that l-Gov, but not d-Gov, would block the PPI impairments caused by apomorphine, consistent with its strong dopamine D2L receptor antagonist activity. The heterogeneity of antipsychotic drug effects on the MK-801-induced disruption of PPI in previous reports made it difficult to develop a clear a priori hypothesis regarding the effects of d- or l-Gov in this paradigm. We also measured the effects of all drugs on the startle response and prepulse-elicited reactivity (Yee and Feldon 2009). Given the effectiveness of l-Gov in blocking the PPI impairments caused by apomorphine and MK-801, we also conducted a dose-response experiment of the effects of l-Gov (0.3, 1.0, 3.0 mg/kg) alone on PPI.

Methods

Animals

Adult male Long-Evans rats (Charles River Laboratories, Quebec, Canada) weighing 325–500 g throughout the course of testing were group housed (two per cage) in standard polypropylene cages in a temperature-controlled (21 °C) colony room on a 12:12 h light/dark cycle with food (Purina Rat Chow) and water available ad libitum. Experimental procedures were carried out during the light phase (lights on at 0700 hours). All experimental procedures were conducted in accordance with the Canadian Council on Animal Care and were approved by the University of Saskatchewan Animal Research Ethics Board.

Drug preparation

Apomorphine (0.2 mg/kg, Howland et al. 2004; Sigma, St. Louis, MO) was dissolved in 0.1% ascorbic acid in water. MK-801 (0.15 mg/kg; Lins et al. 2015; Abcam, Toronto, Ontario) was dissolved in water. $_{d}$- and $_{l}$-Gov were synthesized by the Sammis Lab (Department of Chemistry, University of British Columbia) and dissolved in a 1 mg/mL solution of 50% dimethyl sulfoxide (DMSO; Sigma, St. Louis, MO) and 50% water. Each drug was administered at a volume of 1 mL/kg bodyweight. Initially, we elected to use a single dose of $_{d}$- and $_{l}$-Gov based on previous findings reporting dose-response effects of govadine in several paradigms associated with symptoms of psychotic behavior. In these cases, in the absence of drug effect at a dose of 1.0 mg/kg, doses up to 10 times greater also failed to yield effects (Lapish et al. 2014). A recent study by our group on the effects of each enantiomer of govadine in a visual-spatial learning and memory task showed $_{l}$-Gov (1.0 but not 0.3 or 3.0 mg/kg) effectively reversed MK-801 induced impairments whereas $_{d}$-Gov had no effect at doses up to 3.0 mg/kg (Lins et al. 2015). Based on these data, we chose to administer 1.0 mg/kg of each enantiomer in conjunction with apomorphine and MK-801 to assess effects on PPI and startle reactivity. Positive effects of $_{l}$-Gov (1.0 mg/kg) encouraged a separate dose-response experiment with $_{l}$-Gov (0.3, 1.0, and 3.0 mg/kg) alone using the same PPI protocol. It should be noted that the use of a single dose of Gov with apomorphine and MK-801 is a limitation for the study and a full dose-response characterization of the effects of $_{d}$- and $_{l}$-Gov on disrupted PPI would be valuable.

Behavioral testing

Rats were handled in small groups for 5 min/day at least three times before the first PPI session. The PPI testing procedure was conducted according to a previously published protocol (Howland et al. 2012; Ballendine et al. 2015). Two SR-Lab startle boxes (San Diego Instruments, San Diego, CA, USA) were used. Each testing session began with 5-min acclimatization during which a background noise (70 dB) was presented and remained constant for the entire testing period. After acclimatization, six pulse-alone trials (120 dB, 40 ms) were presented to obtain steady startle amplitude. Following the 6 pulse-alone trials, 84 trials of three types were presented in pseudorandom order: pulse-alone (6 trials; 120 dB, 40 ms); prepulse + pulse (72 trials; parameters described below); or no stimulus (6 trials). Prepulse + pulse trials began with a 20-ms prepulse of 3, 6, or 12 dB above background noise (70 dB). Four different prepulse—pulse intervals of 30, 50, 80, or 140 ms—were used between the onset of the prepulse and the onset of the 120-dB pulse. Six trials of each prepulse × prepulse-pulse interval combination were presented. Each testing session ended with another six pulse-alone trials (120 dB, 40 ms). The inter-trial interval varied from 3 to 14 s (average 7.5 s) in random order. After each session, the startle boxes were cleaned with 40% ethanol.

In experiment one, rats ($n = 20$) received six treatments in a counterbalanced, Latin square, within-subjects design: vehicle, $_{d}$-Gov, $_{l}$-Gov, apomorphine, apomorphine + $_{d}$-Gov, and apomorphine + $_{l}$-Gov. Govadine was administered 15 min prior to apomorphine which was given immediately prior to PPI (Howland et al. 2004). In experiment two, a separate group of rats ($n = 19$) was tested similarly to experiment one using the following treatments: vehicle, $_{d}$-Gov, $_{l}$-Gov, MK-801, MK-801 + $_{d}$-Gov, and MK-801 + $_{l}$-Gov. Govadine was administered immediately prior to MK-801, 15 min before starting PPI (Lapish et al. 2014; Lins et al. 2015). In experiment three, a third cohort of rats ($n = 12$) was tested in the same PPI protocol using three doses of $_{l}$-Gov (0.3, 1.0, and 3.0 mg/kg) as well as vehicle injections 15 min prior to PPI. All injections were administered via the subcutaneous (s.c.) route except for MK-801 which was administered intraperitoneally (i.p.). In all experiments, PPI sessions were conducted every 3–4 days until all treatments were complete. Repeated treatments with apomorphine or MK-801 were administered a minimum of 6 days apart to reduce potential sensitization effects.

Data analyses

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21 for Windows (IBM, Chicago, IL). Greenhouse-Geisser corrections were used for instances of sphericity violations (Mauchley's Test) for all repeated measures analysis of variance (ANOVA) with no adjustments otherwise. Post hoc analyses were performed using Tukey's test. Statistical significance for all comparisons was $p \leq 0.05$. PPI was calculated by averaging the startle amplitudes for each trial type, and the percent PPI for each prepulse intensity was calculated using the formula:

[100 − (100 × startle amplitude on prepulse + pulse trials)/(startle amplitude on pulse-alone trials)]. PPI was observed for the 50-, 80-, and 140-ms interval whereas the 30-ms interval produced prepulse facilitation. Therefore, data for the 30-ms interval were analyzed separately from the other intervals (Howland et al. 2012; Ballendine et al. 2015). The data from both experiments 1 and 2 were first analyzed with repeated measures ANOVAs (drug treatment, $_{d}$-Gov or $_{l}$-Gov, prepulse-pulse interval and prepulse intensity as factors). Additional analysis was conducted on experiment 2 data with separate ANOVAs where $_{d}$-Gov and $_{l}$-Gov were analyzed separately. The data from experiment 3 was analyzed with a repeated measure ANOVA ($_{l}$-Gov dose, prepulse-pulse interval and prepulse intensity as factors). Startle data were analyzed with repeated measures ANOVAs (drug treatment, $_{d}$-Gov or $_{l}$-Gov, and pulse block as factors for experiments 1 and 2 or $_{l}$-Gov dose and pulse block as factors for experiment 3) for each experiment. Non-significant main effects and interactions are not reported.

Results

Disruption of PPI by apomorphine is blocked by $_{l}$-Gov but not $_{d}$-Gov

Startle As shown in Fig. 1a, rats displayed robust startle to presentation of the 120-dB tones following all treatments. A significant main effect of pulse block was observed ($F_{(1.03,19.56)} = 44.15$, $p < 0.001$) indicating habituation of startle over the testing session. None of the drug treatments affected startle (statistics for interactions not shown).

We also assessed the effects of the treatments on baseline reactivity during trials in which no stimulus was presented or the prepulses (3, 6, 12 dB) were presented alone (Fig. 1b). All animals demonstrated increased reactivity to louder prepulse stimuli ($F_{(2.04,38.75)} = 3.80$, $p = 0.030$). Significant main effects of both apomorphine ($F_{(1,19)} = 73.78$, $p < 0.001$) and Gov ($F_{(2,38)} = 17.07$, $p < 0.001$) on reactivity were found. These main effects were qualified by a significant apomorphine by Gov interaction ($F_{(1.48,28.10)} = 4.72$, $p = 0.026$) that showed startle reactivity only significantly increased with the apomorphine and apomorphine + $_{d}$-Gov treatments but not with the apomorphine and $_{l}$-Gov treatments.

PPI Rats in all treatment conditions displayed varying levels of PPI (Fig. 2a, b) that were determined by both prepulse-pulse interval ($F_{(2,38)} = 19.45$, $p < 0.001$) and prepulse intensity ($F_{(1.34,25.52)} = 180.02$, $p < 0.001$). The main effects of apomorphine ($F_{(1,19)} = 5.18$, $p = 0.035$) and Gov ($F_{(2,38)} = 6.10$, $p = 0.005$) were both statistically significant. A significant apomorphine by Gov interaction qualified these main effects ($F_{(2,38)} = 5.60$, $p = 0.007$) and revealed disrupted PPI in apomorphine-treated animals relative to vehicle-, $_{l}$-Gov-, and apomorphine + $_{l}$-Gov-treated animals collapsed across all prepulse-pulse intervals and prepulse intensities (Fig. 2a; $p < 0.05$). Overall, $_{d}$-Gov significantly decreased PPI relative to $_{l}$-Gov (Fig. 2a; $p < 0.05$). Prepulse-pulse interval did not significantly interact with any of the treatment groups (all $p > 0.05$) and thus the means were collapsed across prepulse-pulse interval (Fig. 2b). A significant apomorphine by Gov by prepulse intensity interaction ($F_{(4,76)} = 2.52$, $p = 0.048$) revealed the effects of apomorphine and $_{d}$- or $_{l}$-Gov depended on the prepulse intensity (Fig. 2b). Post hoc analyses revealed that at the 3-dB prepulse intensity apomorphine treatment significantly impaired PPI relative to vehicle, $_{d}$-Gov, $_{l}$-Gov, and apomorphine + $_{l}$-Gov treatments ($p < 0.05$). Also, apomorphine + $_{d}$-Gov significantly reduced PPI relative to the vehicle treated animals ($p < 0.05$). At the 6-dB prepulse intensity, apomorphine, $_{d}$-Gov, and apomorphine + $_{d}$-Gov treatments all significantly reduced PPI relative to vehicle treatment ($p < 0.05$). At the 12-dB intensity, apomorphine and apomorphine + $_{d}$-Gov treatments significantly reduced PPI relative to vehicle treatment ($p < 0.05$).

When trials conducted with the 30-ms interval were examined (Fig. 3a), significant main effects of prepulse intensity ($F_{(1.49,28.21)} = 42.26$, $p < 0.001$) and apomorphine were found ($F_{(1,19)} = 5.12$, $p = 0.036$). A significant apomorphine by prepulse intensity interaction ($F_{(1.54,29.28)} = 4.44$, $p = 0.029$) followed up by post hoc analysis revealed that regardless of treatment with either govadine enantiomer, apomorphine significantly reduced PPI relative to non-apomorphine-treated animals for the 3- and 6-dB intensities ($p < 0.05$). Post hoc tests also demonstrated that significant PPI facilitation was observed for all treatments at the 12 dB prepulse intensity relative to the 3 and 6 dB intensities ($p < 0.05$).

PPI impairments caused by MK-801 are reversed by $_{l}$-Gov but not $_{d}$-Gov

Startle Similar to results observed for the apomorphine-treated rats, habituation of startle to the pulse was confirmed by significant main effects of pulse block (Fig. 1c; $F_{(1.06,19.15)} = 64.78$, $p < 0.001$). A significant main effect of MK-801 ($F_{(1,18)} = 30.51$, $p < 0.001$) and a significant MK-801 by pulse block interaction ($F_{(1.17,21.08)} = 11.40$, $p = 0.002$) revealed MK-801 treatment only significantly increased startle during the first block of startle-alone trials, but not during the second or third block ($p < 0.05$). A significant main effect of Gov ($F_{(2,36)} = 6.67$, $p = 0.003$) was also found. Collapsed across MK-801 treatment, $_{l}$-Gov significantly decreased startle relative to $_{d}$-Gov and vehicle treatment ($p < 0.05$).

When reactivity on trials with no stimulus or 3-, 6-, or 12-dB prepulses alone was examined (Fig. 1d), reactivity significantly increased across all groups as prepulse-alone intensity

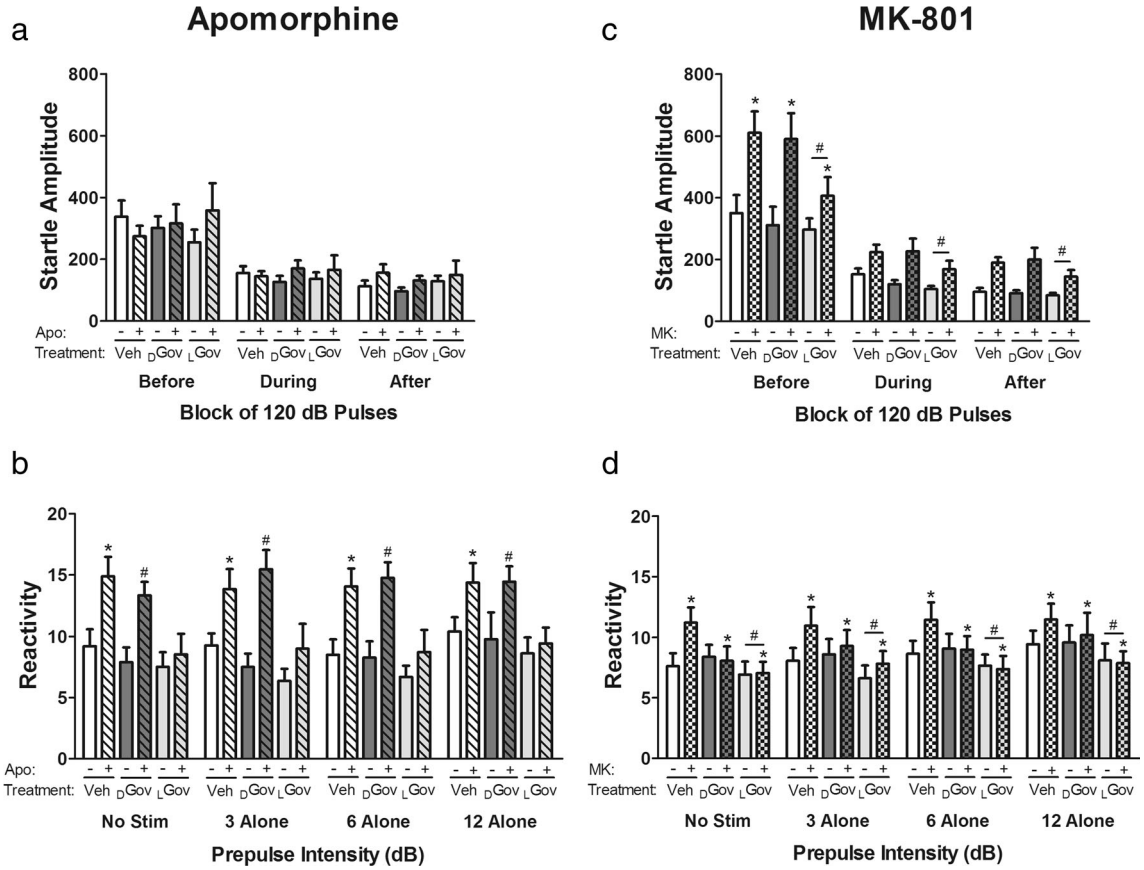

Fig. 1 Effects of $_{d}$- and $_{l}$-govadine (Gov) (1.0 mg/kg) on startle and its modulation by apomorphine (Apo) or MK-801 (MK). Amplitude of startle (arbitrary units) when rats were treated with Apo (0.2 mg/kg) and $_{d}$- -or $_{l}$-Gov (**a**). Neither Apo nor either enantiomer of Gov affected startle (arbitrary units) before, during, or after the PPI trials were presented. The effects of Apo and each enantiomer of Gov on reactivity during the no stimulus and 3-, 6-, and 12-dB prepulse-alone trials (**b**). Reactivity was significantly increased by Apo (*$p < 0.05$). $_{D}$-Gov had no effect on the Apo-elicited increase while (#$p < 0.05$) $_{l}$-Gov significantly reduced it. Amplitude of acoustic startle (arbitrary units) when rats were treated with MK (0.15 mg/kg) and $_{d}$- -or $_{l}$-Gov (**c**). MK-801 treatment significantly increased the startle during the first block of pulse-alone trials, but not during the second or third block (*$p < 0.05$). Collapsed across MK treatment, $_{l}$-Gov significantly decreased startle relative to $_{d}$-Gov and vehicle treatments (#$p < 0.05$). The effects of MK and each enantiomer of govadine on reactivity during the no stimulus and 3-, 6-, and 12-dB prepulse-alone trials (**d**). Regardless of Gov treatment, MK-801 treatment significantly increased reactivity (*$p < 0.05$). Collapsed across MK-801 treatment, $_{l}$-Gov significantly decreased reactivity relative to vehicle and $_{d}$-Gov treatments (#$P < 0.05$)

increased ($F_{(3,54)} = 4.89$, $p = 0.004$). A significant main effect of MK-801 revealed that, regardless of Gov treatment, MK-801 treatment significantly increased reactivity ($F_{(1,18)} = 4.57$, $p = 0.046$). A significant main effect of Gov ($F_{(2,36)} = 8.95$, $p = 0.001$) was also observed. Post hoc analyses revealed that collapsed across MK-801 treatment, $_{l}$-Gov significantly decreased reactivity relative to vehicle and $_{d}$-Gov treatment ($p < 0.05$).

PPI Significant main effects of prepulse-pulse interval ($F_{(1.48,26.67)} = 6.29$, $p = 0.010$) and prepulse intensity ($F_{(1.49,26.74)} = 216.19$, $p < 0.001$) indicate that all animals displayed different levels of PPI for the varying levels of interval and intensity (Fig. 2c, d). As prepulse-pulse interval did not significantly interact with any of the treatment groups (all $p > 0.05$), the remaining means and analyses were collapsed across prepulse-pulse interval. Significant main effects of MK-801 ($F_{(1,18)} = 14.54$, $p = 0.001$) and MK-801 by intensity interaction ($F_{(2,36)} = 9.18$, $p = 0.001$) were found (Fig. 2d). As is well established, MK-801 disrupted PPI in a manner that was significantly related to the prepulse intensity (Reijmers and Peeters 1994; Vorhees et al. 1996). MK-801 impaired PPI at the 3- and 6-dB prepulse intensity, but not at the 12-dB intensity ($p < 0.05$).

In the omnibus ANOVA, the main effect of Gov ($F_{(2,36)} = 3.05$, $p = 0.060$) and MK-801 by Gov interaction ($F_{(2,36)} = 2.68$, $p = 0.082$) failed to reach significance; however, inspection of the graphical results appeared to indicate an effect of $_{l}$-Gov on MK-801 disrupted PPI. Due to increased risk of type II error as a result of multiple comparisons in the omnibus ANOVA, we performed a secondary repeated measure ANOVA which assessed the effects of each Gov enantiomer on PPI separately. Dissociable effects of the enantiomers on the MK-801-

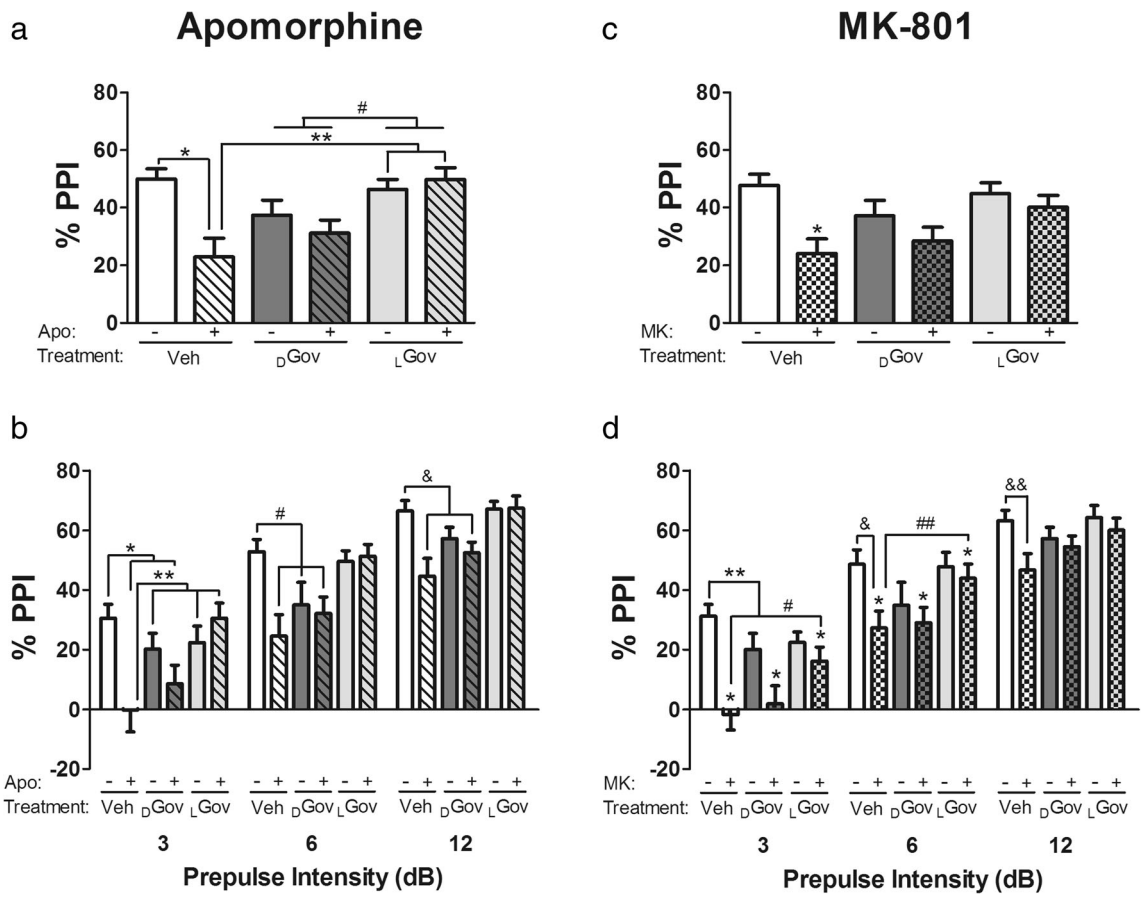

Fig. 2 Percent PPI displayed for the tests when rats were treated with either Apo and $_{d}$-Gov or $_{l}$-Gov, or MK and $_{d}$-Gov or $_{l}$-Gov. Data are displayed for the average across prepulse intensity and prepulse-pulse interval with Apo and $_{d}$-Gov or $_{l}$-Gov (**a**). Apo treatment disrupted PPI relative to vehicle (*$p < 0.05$), $_{l}$-Gov and Apo + $_{l}$-Gov (**$p < 0.05$) treated animals collapsed across all prepulse-pulse intervals and prepulse intensities. Overall, $_{d}$-Gov significantly decreased PPI relative to $_{l}$-Gov (#$p < 0.05$). The effects of Apo and $_{d}$- -or $_{l}$-Gov on PPI at the 3-, 6-, and 12-dB prepulse intensities averaged across prepulse-pulse interval (**b**). At the 3-dB prepulse intensity, Apo treatment significantly impaired PPI relative to vehicle (*$p < 0.05$), $_{d}$-Gov, $_{l}$-Gov, and Apo + $_{l}$-Gov treatments (**$p < 0.05$). Also, Apo + $_{d}$-Gov significantly reduced PPI relative to vehicle treatment (*$p < 0.05$). At the 6-dB prepulse intensity, Apo, $_{d}$-Gov, and Apo + $_{d}$-Gov treatments all significantly reduced PPI relative to vehicle treatment (#$p < 0.05$). At the 12-dB intensity, Apo and Apo + $_{d}$-Gov treatments significantly reduced PPI relative to vehicle treatment (&$p < 0.05$). PPI averaged across prepulse intensity and prepulse-pulse interval with MK and $_{d}$-Gov or $_{l}$-Gov (**c**). MK significantly reduced PPI relative to vehicle treatment (*$p < 0.05$). The effects of MK and $_{d}$- -or $_{l}$-Gov on PPI at the 3-, 6-, and 12-dB prepulse intensities averaged across prepulse-pulse interval (**d**). MK treatment impaired PPI at the 3- and 6-dB prepulse intensity, but not at the 12-dB intensity (*$p < 0.05$). At the 3-dB prepulse intensity, MK and MK + $_{l}$-Gov treatments resulted in significantly reduced PPI relative to vehicle treatment (**$p < 0.05$). MK + $_{l}$-Gov treatment resulted in increased PPI relative to MK treatment alone (#$p < 0.05$). At the 6-dB intensity, MK significantly reduced PPI relative to both vehicle (&$p < 0.05$) and MK + $_{l}$-Gov treatment (##$p < 0.05$). At the 12-dB intensity, MK significantly reduced PPI compared to vehicle treatment (&&$p < 0.05$)

induced disruption of PPI were apparent. Inspection of the results for the $_{d}$-Gov enantiomer produced the same effects observed for the omnibus ANOVA, specifically, a main effect of MK-801 ($F_{(1,18)} = 12.88$, $p = 0.002$), a main effect of prepulse-pulse interval ($F_{(2,36)} = 4.49$, $p = 0.018$), a main effect of prepulse intensity ($F_{(2,36)} = 200.12$, $p < 0.001$), and an MK-801 by prepulse intensity interaction ($F_{(2,36)} = 10.00$, $p < 0.001$). Inspection of the $_{l}$-Gov analysis also revealed a main effect of MK-801 ($F_{(1,18)} = 16.09$, $p = 0.001$), a main effect of prepulse-pulse interval ($F_{(2,36)} = 5.84$, $p = 0.006$), a main effect of prepulse intensity ($F_{(2,36)} = 169.36$, $p < 0.001$), and a MK-801 by prepulse intensity interaction ($F_{(2,36)} = 11.00$, $p < 0.001$). Additionally, this analysis revealed a signifi cant MK-801 by $_{l}$-Gov interaction ($F_{(1,18)} = 5.74$, $p = 0.028$) and a significant MK-801 by $_{l}$-Gov by intensity interaction (Fig. 2d; $F_{(1.43,25.8)} = 5.29$, $p = 0.020$). Post hoc analyses indicate that at the 3-dB prepulse intensity, MK-801 and MK-801 + $_{l}$-Gov treatments resulted in significantly reduced PPI relative to vehicle treatment ($p < 0.05$). Further post hocs revealed that MK-801 + $_{l}$-Gov treatment resulted in increased PPI relative to MK-801 treatment alone ($p < 0.05$). At the 6-dB intensity, MK-801 significantly reduced PPI relative to both vehicle

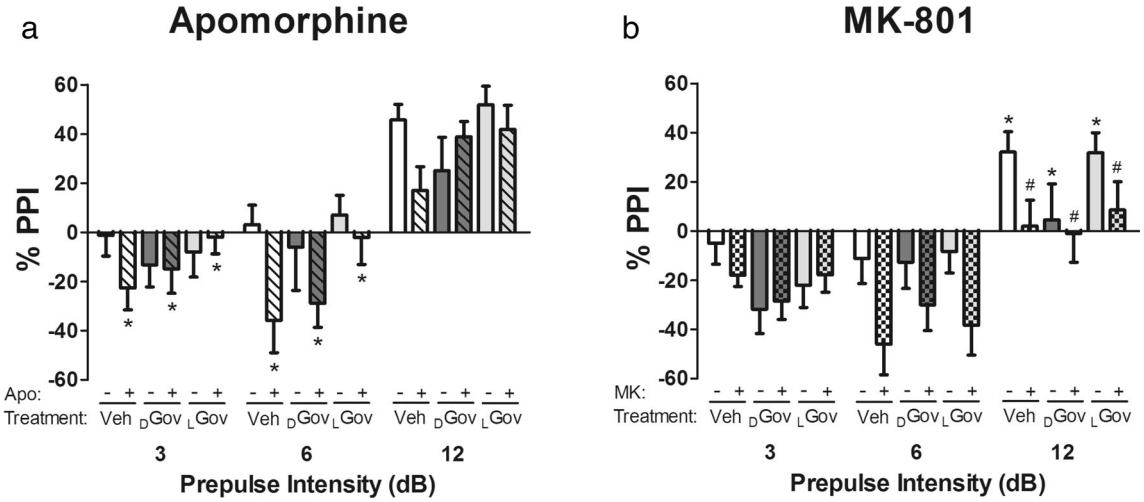

Fig. 3 Percent PPI on short-interval trials for which a 30-ms prepulse-pulse interval was used when rats were treated with either Apo and $_{d}$-Gov or $_{l}$-Gov (**a**) or MK and $_{d}$-Gov or $_{l}$-Gov (**b**). Apo significantly reduced PPI relative to non-Apo treated animals for the 3- and 6-dB intensities (*$p < 0.05$) (**a**). Collapsed across Gov treatments, PPI facilitation was observed in the vehicle animals at the 12-dB intensity relative to the 3-dB intensity (*$p < 0.05$) (**b**). MK treatment collapsed across all Gov treatments resulted in PPI facilitation at the 12-dB intensity relative to the 6-dB intensity (#$p < 0.05$)

and MK-801 + $_{l}$-Gov treatment ($p < 0.05$). At the 12-dB intensity, post hoc analysis revealed that MK-801 significantly reduced PPI compared to vehicle treatment ($p < 0.05$).

Analysis of the 30-ms interval (Fig. 3b) revealed a significant main effect of prepulse intensity ($F_{(2,36)} = 51.41$, $p < 0.001$) and MK-801 ($F_{(1,18)} = 12.25$, $p = 0.003$). Post hoc analysis of a significant prepulse intensity by MK-801 interaction ($F_{(2,36)} = 4.06$, $p = 0.026$) indicated that, collapsed across Gov treatment, PPI facilitation was observed in the vehicle animals at the 12-dB intensity relative to the 3-dB intensity. Alternatively, MK-801 treatment collapsed across all Gov treatments resulted in a shift towards PPI facilitation at the 12-dB intensity relative to the 6-dB intensity. Further analysis of the 30-ms data revealed a significant prepulse intensity by Gov interaction ($F_{(4,72)} = 2.90$, $p = 0.028$); however, no meaningful changes in PPI produced by Gov treatment were observed at varying levels of prepulse intensity.

Dose-dependent effects of $_{l}$-Gov on startle and PPI

Startle Consistent with results obtained for the apomorphine and MK-801-treated rats, habituation of startle to the tone was observed (Fig. 4a; main effect of pulse block: $F_{(2,22)} = 53.81$, $p < 0.001$). A significant main effect of treatment ($F_{(3,33)} = 5.75$, $p = 0.003$) revealed that the 1.0 and 3.0 mg/kg doses of $_{l}$-Gov significantly decreased startle amplitude relative to vehicle treatment ($p < 0.05$).

Examination of startle reactivity to the no stimulus or 3-, 6-, or 12-dB prepulses alone (Fig. 4b) showed a significant main effect of treatment ($F_{(1.72,18.88)} = 10.44$, $p = 0.001$). Post hoc analyses revealed that the 1.0 and 3.0 mg/kg doses of $_{l}$-Gov produced significantly decreased reactivity to all prepulse intensities relative to vehicle treatment ($p < 0.05$). Analyses further revealed that 3.0 mg/kg of $_{l}$-Gov also significantly decreased reactivity relative to the 0.3 mg/kg dose ($p < 0.05$).

PPI Similar to the first two experiments, significant main effects of prepulse-pulse interval ($F_{(2,22)} = 4.54$, $p = 0.22$); prepulse intensity ($F_{(2,22)} = 374.00$, $p < 0.001$); and a significant prepulse-pulse interval by prepulse intensity interaction ($F_{(2.18,24.01)} = 9.29$, $p = 0.001$) demonstrate that all animals had varying degrees of PPI across the levels of interval and intensity (Fig. 4d). Prepulse-pulse interval did not significantly interact with $_{l}$-Gov dose ($p > 0.05$). However, a significant main effect of treatment ($F_{(3,33)} = 4.11$, $p = 0.014$) and an interaction between treatment and prepulse intensity (Fig. 4d; $F_{(6,66)} = 3.32$, $p = 0.006$) were found. A significant treatment by prepulse-pulse interval by prepulse intensity interaction was also observed ($F_{(12,132)} = 2.23$, $p = 0.014$). Post hoc analyses revealed that at the 3-dB intensity, treatment with 0.3 mg/kg of $_{l}$-Gov significantly decreased PPI relative to the 1.0 and 3.0 mg/kg doses ($p < 0.05$).

Analysis of the 30-ms interval trials (Fig. 4e) revealed a significant main effect of prepulse intensity ($F_{(1.36,14.98)} = 88.66$, $p < 0.001$) and treatment ($F_{(3,33)} = 3.74$, $p = 0.020$). Although all treatment groups showed increasing evidence of PPI as prepulse intensity increased, rats treated with 3.0 mg/kg of $_{l}$-Gov showed consistently higher PPI overall relative to animals treated with 0.3 mg/kg of $_{l}$-Gov ($p < 0.05$).

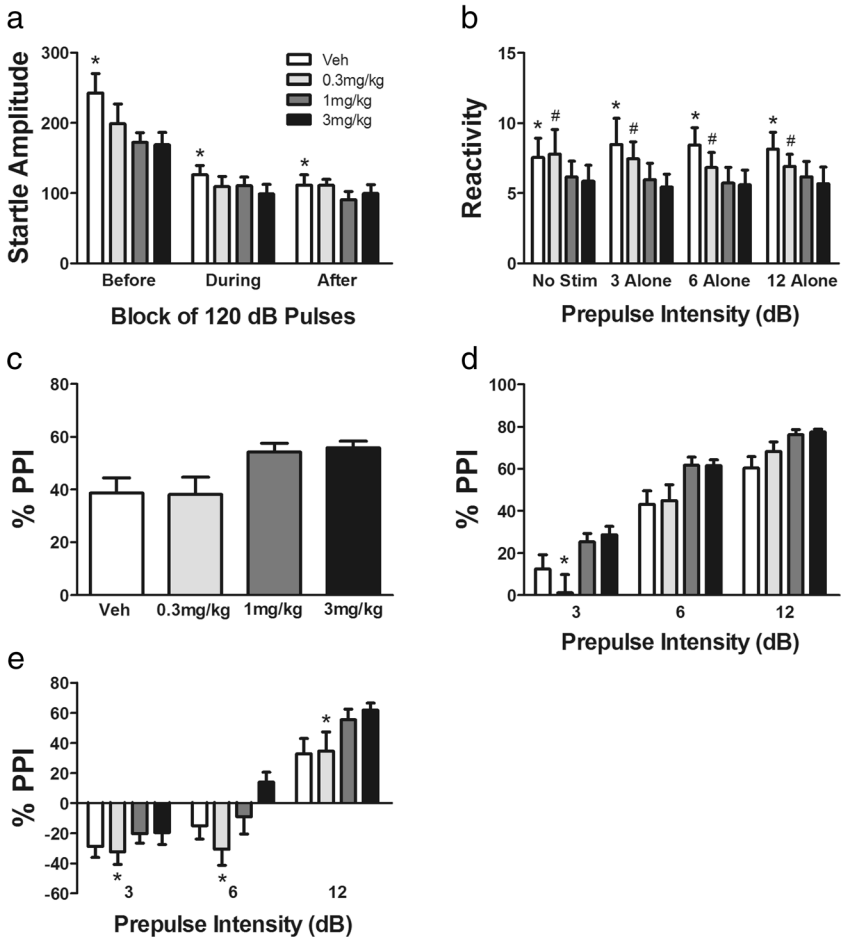

Fig. 4 Effects of $_{l}$-govadine (Gov) (0.3, 1.0, 3.0 mg/kg) or vehicle on startle, startle reactivity, percent PPI long-interval trials, and percent PPI short-interval trials. Amplitude of startle (arbitrary units) when rats were treated with varying doses of $_{l}$-Gov (**a**). Both the 1.0 and 3.0 mg/kg dose of $_{l}$-Gov significantly decreased startle before, during, and after the PPI trials were presented (*$p < 0.05$). The effects of $_{l}$-Gov dose on reactivity during the no stimulus and 3-, 6-, and 12-dB prepulse-alone trials (**b**). Both the 1.0 and 3.0 mg/kg dose of $_{l}$-Gov significantly decreased reactivity relative to vehicle treatment during the no stimulus and all prepulse-alone trials (*$p < 0.05$). The 3.0 mg/kg dose of $_{l}$-Gov also significantly decreased reactivity relative to the 0.3 mg/kg dose across all trials (#$p < 0.05$). Average PPI across all prepulse-pulse intervals and prepulse intensities for each dose of $_{l}$-Gov (**c**). The effects of each dose of $_{l}$-Gov on PPI at the 3-, 6-, and 12-dB prepulse intensities averaged across prepulse-pulse interval (**d**). The 0.3 mg/kg dose of $_{l}$-Gov resulted in significantly decreased PPI relative to the 1.0 and 3.0 mg/kg doses at the 3 dB intensity (*$p < 0.05$). Percent PPI for the 30 ms prepulse-pulse intervals when rats were treated with each dose of $_{l}$-Gov (**e**). Averaged across all prepulse intensities, the 0.3 mg/kg dose of $_{l}$-Gov significantly decreased PPI relative to the 3.0 mg/kg dose (*$p < 0.05$)

Discussion

The present study tested the effects of the $_{d}$- and $_{l}$- enantiomers of govadine on PPI alone and when disrupted by apomorphine and MK-801. Apomorphine disrupted PPI (Fig. 2) without significant effects on startle (Fig. 1) whereas MK-801 increased startle (Fig. 1) and also disrupted PPI (Fig. 2). Interestingly, both drugs increased reactivity during trials in which a pulse was not presented (Fig. 1), effects which were blocked by $_{l}$-Gov, but not $_{d}$-Gov. $_{l}$-Gov, but not $_{d}$-Gov, blocked the disruptive effects of apomorphine (Fig. 2) and MK-801 (Fig. 2) on PPI at varying prepulse intensities (3, 6, and 12 dB). As previously reported, trials with a short prepulse-pulse interval (30 ms) had low levels of PPI, particularly for trials with 3- and 6-dB prepulses (Fig. 3). MK-801 and apomorphine tended to reduce PPI for these trials. The enantiomers of govadine did not significantly affect PPI on short-interval trials; however, $_{d}$-Gov alone significantly disrupted PPI at the long-interval relative to $_{l}$-Gov. Taken together, these results suggest that $_{l}$-Gov functions much like atypical

antipsychotic drugs in blocking the effects of apomorphine and MK-801 on PPI (Swerdlow and Geyer 1993).

The effects of apomorphine and MK-801 on PPI in Long-Evans rats

The PPI protocol employed in the present experiments used a range of intervals between prepulses and the startling pulse because previous research has shown interval-specific effects of some manipulations (Fendt et al. 2001; Jones and Shannon 2000; Pinnock et al. 2015; Yeomans et al. 2010). Our results for the long-interval trials (50, 80, 140 ms between the prepulse and pulse) confirm the well-documented impairments of PPI caused by the direct dopamine D2R agonist apomorphine and NMDA receptor antagonist MK-801 in previous studies using long prepulse-pulse intervals (Geyer et al. 2001). Previous studies have shown that hooded rats, including the Long-Evans (used here) and Lister strains, are less sensitive to the disruptive effects of apomorphine but not MK-801 on PPI than the Sprague-Dawley and Wistar strains (Kinney et al. 1999; Swerdlow et al. 2000; Weiss et al. 2000; Qu et al. 2009). We observed a robust disruption in PPI following apomorphine treatment. This was observed using a moderate dose of apomorphine (0.2 mg/kg) which has been shown to impair PPI in Long-Evans rats in some studies (Howland et al. 2004) but not others (Swerdlow et al. 2001b). Short-interval trials (30-ms prepulse-pulse interval) were characterized by lower PPI than long-interval trials, particularly for the trials with 3- and 6-dB prepulses. We and others have observed this pattern previously (Swerdlow et al. 2000; van den Buuse and Gogos 2007; Jones et al. 2010; Howland et al. 2012; Ballendine et al. 2015). Interestingly, startle was in fact increased during short-interval prepulse-pulse trials (i.e., a form of prepulse facilitation) following MK-801 and apomorphine consistent with previous studies using MK-801 (al-Amin and Schwarzkopf 1996; Brosda et al. 2011) or ketamine (Mansbach and Geyer 1991) with short intervals between prepulse and pulse.

MK-801 (0.15 mg/kg) significantly increased the startle to the 120-dB pulse throughout the test session, an effect that has been reported previously following the same dose in Sprague-Dawley and Wistar rats (Varty et al. 1999 but see also Wiley et al. 2003). Interestingly, startle reactivity on no-stimulus and prepulse-alone trials was significantly enhanced by both apomorphine and MK-801. Others have reported no effect of apomorphine on reactivity in Long-Evans rats (Swerdlow et al. 2001b) although increased reactivity has been noted in Sprague-Dawley rats (Swerdlow et al. 2001b; Swerdlow et al. 2004) and C57BL6 mice (Yee et al. 2004b). The effects of NMDA receptor antagonists on prepulse-elicited reactivity have not been consistent with the enhancement produced by apomorphine (Yee et al. 2004a; Yee and Feldon 2009) although to the best of our knowledge, the effects of MK-801 on prepulse-elicited reactivity in rats have not been reported previously. The increase in reactivity caused by apomorphine and MK-801 may reflect a generalized increase in locomotor behavior caused by these drugs. Interestingly, $_{l}$-Gov has been shown previously to block amphetamine-induced locomotion (Lapish et al. 2014). Therefore, testing the effects of $_{l}$-Gov on locomotor behavior induced by apomorphine or MK-801 in an open field may show a generalized effect of $_{l}$-Gov on locomotor behavior caused by a range of psychotomimetic drugs.

Selective effects of the $_{d}$- and $_{l}$- enantiomers of govadine on the disruptions in PPI induced by apomorphine and MK-801

Previous studies have demonstrated that $_{l}$-Gov induces deficits in conditioned avoidance responding and attenuates amphetamine-induced locomotion (Lapish et al. 2014). In contrast, $_{d}$-Gov has no such effects; however, it improves working memory and temporal order memory. Despite these differences in cognitive and behavioral effects, both enantiomers act to improve social interaction and latent inhibition in animal models of schizophrenia (Lapish et al. 2012, 2014). The present results are novel and show that $_{l}$-Gov blocks the disruptive effect of either apomorphine or MK-801 on PPI. As well, $_{l}$-Gov reduces the apomorphine- and MK-801-induced increases in reactivity. $_{d}$-Gov has no effect on these measures, although it did reduce PPI for long-interval trials. While the mechanism underlying the reduction in PPI following $_{d}$-Gov will be difficult to discern, it may relate to the enantiomer's unique effects on dopamine release and receptor antagonism (Lapish et al. 2014). Well-documented side effects of typical antipsychotics are extrapyramidal symptoms (EPS) which include Parkinsonism, dystonia, akathisia, and tardive dyskinesia (Porsolt et al. 2010). In rodents, catalepsy is a common behavioral measure used to assess the potential for a neuroleptic drug to induce EPS (Porsolt et al. 2010; Lapish et al. 2014). In a previous study $_{l}$-Gov, but not $_{d}$-Gov, induced catalepsy in a dose-dependent manner; however, minimal effects were observed at 0.3 and 1.0 mg/kg with an increase in immobility at the 3.0 mg/kg dose. This effect is consistent with its profile as a putative antipsychotic and D2 antagonist (Lapish et al. 2014). In the dose-response study (Fig. 4), 1.0 and 3.0 mg/kg of $_{l}$-Gov reduced startle reactivity, which may reflect a generalized effect on locomotor activity consistent with effects reported for haloperidol and clozapine by Hoffman et al. (1993). However, dose-dependent changes in PPI were relatively subtle, while a non-significant increase in PPI was noted following higher doses of $_{l}$-Gov, an effect

also found with haloperidol (Hoffman et al. 1993). Disrupted PPI following apomorphine treatment has been linked to activation of the mesolimbic DA system (Geyer et al. 2001). Consistent with this theory are findings showing that typical antipsychotic drugs such as haloperidol, which are potent D2 receptor antagonists, block the effects of apomorphine on PPI (Swerdlow and Geyer 1993; Geyer et al. 2001). Thus, the effects of $_{l}$-Gov on the apomorphine-induced disruption of PPI may be attributable to its demonstrated similarity to typical antipsychotics, as an antagonist with high affinity for D2 receptor and its effects in behavioral assays such as conditioned avoidance responding (Lapish et al. 2014). In keeping with this theory, the failure of $_{d}$-Gov to block the effect of apomorphine on PPI may be related to its relatively lower affinity for D2 receptors.

In contrast to the reversal of apomorphine-induced PPI impairment, typical antipsychotics such as haloperidol do not block PPI impairment when induced by MK-801 (Keith et al. 1991; Hoffman et al. 1993; Bast et al. 2000). Therefore, the D2 receptor antagonism caused by $_{l}$-Gov is not a likely explanation for the reversal of the MK-801-induced PPI impairment. In some studies, atypical antipsychotics such as clozapine block the effects of acute MK-801 (or other NMDA receptor antagonists) on PPI (Bubenikova et al. 2005; Geyer et al. 2001; Bakshi et al. 1994; but see Bast et al. 2000; Hoffman et al. 1993) raising the possibility that serotonin and/or muscarinic receptor mechanisms may be involved. At psychotomimetic doses, non-competitive NMDAR antagonists such as MK-801 disrupt neural circuits by reducing GABAergic transmission which leads to disinhibition of pyramidal neurons and increased midbrain dopamine efflux (Laruelle et al. 1999; Kegeles et al. 2000; Balla et al. 2001, 2003; Homayoun and Moghaddam 2007; Vinson and Conn 2012). $_{l}$-Gov's reversal of the MK-801-induced PPI impairment may be explained by its unique ability to simultaneously enhance DA efflux in the PFC and block D2 receptors (Lapish et al. 2014). Stimulation of D1 receptors increases inhibitory neurotransmission in the PFC while D2 receptor stimulation decreases it (Seamans et al. 2001; Gorelova et al. 2002). Differential DA signaling is regulated in a concentration-dependent manner (Trantham-Davidson et al. 2004). D1 receptor signaling is proposed to cause a prolonged increase in inhibitory postsynaptic current (IPSC) through activation of adenylyl cyclase (AC) and protein kinase A (PKA), which inhibit K^+ channels in parvalbumin-containing interneurons. Blocking D2 receptors in the presence of high dopamine concentration increases inhibitory postsynaptic currents, an effect that is prevented by D1 receptor antagonists (Gorelova et al. 2002). Thus, D2 receptor signaling may occlude D1 receptor signaling during periods of high dopamine concentration and this occlusion can be prevented with D2 antagonism (Gorelova et al. 2002). As $_{l}$-Gov blocks D2 receptors while increasing DA efflux, the resulting increase in D1 receptor binding and signaling may lead to increased PKA and ultimately, increased excitability in parvalbumin-containing interneurons to counteract the effects of MK-801. Such a mechanism is supported by findings that NMDA receptor antagonist-induced PPI deficits are reversed by the GABA receptor agonist baclofen (Bortolato et al. 2004) and D1 receptor agonist A77636 (Bubenikova-Valesova et al. 2009). Additionally, infusion of the GABA-A channel blocker picrotoxin into the medial prefrontal cortex via intracranial cannulae disrupts PPI, and is reversed by pretreatment with haloperidol in Wistar rats (Japha and Koch 1999). It is important to note that this effect may be strain dependent as it was not replicated in Lister hooded rats (Pezze et al. 2014). Activation of D1 receptors also stimulates the translocation of NMDARs to the postsynaptic membrane (Dunah et al. 2004) and secondary messengers which phosphorylate NMDAR subunits to potentiate the NMDA-evoked response (Missale et al. 2006) providing additional mechanisms through which $_{l}$-Gov may reverse the effects of NMDA receptor antagonism. $_{d}$-Gov, which is not a potent D2 receptor antagonist (Lapish et al. 2014), lacks the ability to restore the PPI deficits in both drug conditions.

Conclusion

These data are consistent with the potential use of enantiomers of govadine as treatments for schizophrenia. $_{l}$-Gov, a D2 receptor antagonist which increases DA efflux, was effective in restoring deficits in PPI induced by MK-801 or apomorphine to control levels. In contrast, $_{d}$-Gov, the enantiomer associated with cognitive enhancement, did not reverse the disruption of PPI by either drug. A dose-response study revealed $_{l}$-Gov reduced startle amplitude, reactivity, and PPI in the dose-dependent manner.

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Compliance with ethical standards

Conflict of interest JGH is a CIHR New Investigator. BRL received salary support from the University of Saskatchewan. WNM received salary support from the College of Medicine at the University of Saskatchewan and the Saskatchewan Health Research Foundation. AGP holds a patent for the use of the $_{d,l}$-govadine and its enantiomers as putative antipsychotic drugs. The remaining authors declare no conflict of interest.

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