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Spontaneously Hypertensive Rats (SHR) present deficits in prepulse inhibition of startle specifically reverted by clozapine

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ABSTRACT

Deficits in an operational measure of sensorimotor gating – the prepulse inhibition of startle (PPI) – are presented in psychiatric disorders such as schizophrenia, bipolar disorder, and attention deficit/hyperactivity disorder (ADHD). Some previous studies showed that the spontaneously hypertensive rats (SHR) present PPI deficit. Although SHR is suggested as an animal model to study ADHD, we have suggested that the behavioral phenotype of this strain mimics some aspects of schizophrenia. The aim of this study was to characterize the PPI response in SHR. Pharmacological characterization consisted in the evaluation of the effects of the following drugs administered to adult Wistar rats (WR) and SHR previously to the PPI test: amphetamine (used for ADHD and also a psychotomimetic drug), haloperidol and clozapine (antipsychotic drugs), metoclopramide (dopamine antagonist without antipsychotic properties) and carbamazepine (mood stabilizer). Our results showed that SHR presented reduced PPI. This deficit was similar to that induced by amphetamine in WR. Only the atypical antipsychotic clozapine improved the PPI deficit observed in SHR. These findings reinforce the SHR strain as an animal model to study several aspects of schizophrenia, including the abnormalities in sensorimotor gating associated with this disease.

1. Introduction

Prepulse inhibition of startle (PPI) is characterized by the reduction of an acoustic startle reflex to an intense acoustic stimulus (pulse) when immediately preceded by a lower intensity stimulus (prepulse) (Hoffman and Ison, 1980; Swerdlow et al., 2001). PPI is considered an operational measure of sensorimotor gating and is extensively used in translational models since it appears to be present in all mammals, including rats and humans (Swerdlow et al., 1994, 2000). PPI is reduced in psychiatric disorders such as acute psychotic mania in bipolar disorder (Perry et al., 2001), ADHD (Hawk et al., 2003) and, predominantly, in schizophrenia (Braff et al., 2001; Geyer et al., 2001; Weiss and Feldon, 2001).

In animals, PPI deficits is produced by pharmacological stimuli (Geyer et al., 2001) such as dopaminergic agonists or NMDA receptor antagonists. Several studies have demonstrated that PPI deficits in animal models of schizophrenia display face, construct and predictive validity (Swerdlow et al., 1994) and have been used to screen antipsychotic efficacy (Swerdlow and Geyer, 1998).

SHR have been suggested as a putative animal model of ADHD (Russell, 2007; Sagvolden and Sergeant, 1998). This strain presents behavioral characteristics of ADHD: it has sustained attention problems, shows hyperactivity and impulsivity (Russell, 2007; Sagvolden et al., 1992). Nevertheless, the absence of beneficial effects of psychostimulants (used to treat this disorder) on ADHD-like behaviors in adult SHR (Bizot et al., 2007; Calzavara et al., 2009; Van den Bergh et al., 2006) has been described. In fact, some behavioral changes are even potentiated by these drugs (Calzavara et al., 2009).

In this regard, we have reported that SHR present a deficit in contextual fear conditioning that is specifically reverted by antipsychotic drugs and potentiated by psychostimulants or other proschizophrenia manipulations, such as ketamine administration and sleep deprivation. It is important to note that procedures aimed to facilitate learning were not able to improve this deficit. This strain also does not

Abbreviations: ADHD, Attention Deficit/Hyperactivity Disorder; AMPH, amphetamine; ANOVA, Analysis of Variance; CARBA, Carbamazepine; CLO, Clozapine; HALO, Haloperidol; METO, Metoclopramide; PPI, Prepulse Inhibition of Startle; PP, Prepulse-Pulse; P, Pulse-Alone; SHR, Spontaneously Hypertensive Rats; VEH, Vehicle; WKY, Wistar Kyoto; WR, Wistar Rats.

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express latent inhibition to contextual fear conditioning (Calzavara et al., 2009). In this context, an absence of latent inhibition process has been described for schizophrenia (Gray et al., 1992) and is one of the most used paradigms to study attentional deficits in animal models of schizophrenia (Weiner, 2003). These findings led us to suggest that the deficit in contextual fear conditioning of adult SHR could be a useful animal model to study abnormalities in emotional context processing related to schizophrenia (Calzavara et al., 2009). Furthermore, we have demonstrated recently that SHR present impaired social interaction (that mimics negative symptoms of schizophrenia – Sams-Dodd, 1998; O'Tuathaigh et al., 2010) that is specifically ameliorated by atypical antipsychotics (as seen in the clinic – Miyamoto et al., 2005) and aggravated by amphetamine (Calzavara et al., 2011). In addition, SHR display hyperlocomotion (that mimics positive symptoms of schizophrenia – Powell and Miyakawa, 2006; Lipska and Weinberger, 2000) attenuated by antipsychotics and potentiated by amphetamine (Calzavara et al., 2011). Finally, while the prevalence of tardive dyskinesia, a late side effect of long-term treatment with antipsychotics (Casey, 1987), is decreased in schizophrenia when compared with affective disorders (Gardos and Cole, 1997), we have described that SHR did not develop oral dyskinesia in animal models of tardive dyskinesia (Abílio et al., 2004; Queiroz et al., 1998).

Parallel to that, it's noteworthy that previous studies describe controversial results in relation to PPI in SHR. Some studies show that SHR present PPI deficits when compared to Wistar Kyoto (WKY) (Ferguson and Cada, 2004; Kinkead et al., 2006), to Sprague-Dawley (SD) (Ferguson and Cada, 2004) or to Lewis rats (Vendruscolo et al., 2006). Conversely, other studies demonstrate that PPI tended to be higher in SHR and WKY than in SD rats (Van den Buuse, 2004) or that SHR has intermediate PPI values (Brown-Norway<SHR<SD<WKY — Palmer et al., 2000). However, methodological differences and the absence of a pharmacological characterization complicate the interpretation of these results.

In this context, the aim of the present work was to characterize PPI response in the SHR strain. We evaluated the effects of the following drugs administered previously to the PPI test: amphetamine (used for ADHD and also a psychotomimetic drug), haloperidol and clozapine (typical and atypical antipsychotics, respectively), metoclopramide (dopamine antagonist without antipsychotic properties) and carbamazepine (a mood stabilizer).

2. Methods

2.1. Animals

Male Wistar rats (WR) and SHR, five-month-old, of our own colony were housed under conditions of controlled temperature (22–23 °C) and lighting (12/12 h light/dark cycle, lights on at 07:00 am). Groups of 5 animals were kept in Plexiglas cages (41×34×16.5 cm), with free access to food and water. The animals were maintained in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA. This study was approved by the Ethical Committee of Federal University of Sao Paulo. All rats used were drug-naive before each experiment.

2.2. Drugs

Amphetamine (Sigma — St Louis, USA) and metoclopramide (Le Petit — São Paulo, Brazil) were diluted in 0.9% saline. Haloperidol (Sigma — St Louis, USA) was dissolved in lactic acid and then diluted in distilled water. Clozapine (Novartis — São Paulo, Brazil) was dissolved in acetic acid and then diluted in distilled water. Carbamazepine (Sigma — St Louis, USA) was dissolved in Tween 80 and then diluted in distillated water. Saline or distillated water plus acid lactic or Tween were used as control solution depending on the drugs used in each experiment. All drug solutions were injected intraperitoneally (i.p.) in a volume of 1 ml/kg body weight.

2.3. Apparatus

The rats were placed in a stabilimeter, which consisted of a wire-mesh cage (16.5×5.1×7.6 cm) suspended within a PVC frame (25×9×9 cm) attached to the response platform with four thumb-nail-screws. The stabilimeter and platform were located inside a ventilated plywood sound attenuating chamber (64×60×40 cm). The floor of the stabilimiter consisted of six stainless steel bars 3.0 mm in diameter and spaced 1.5 cm apart. The startle reaction of the rats generated a pressure on the response platform and analogue signals were amplified, digitized and analyzed by a software of the startle measure system (Insight, São Paulo, Brazil), that also controlled other parameters of the session (intensity of the acoustic stimulus, inter-stimulus interval, etc.). Two loudspeakers located 10 cm above the floor, on each lateral side of the acoustic isolation chamber, were used to deliver the prepulse stimulus, the acoustic startle stimulus and continuous background noise (65 dB). Calibration procedures were conducted before the experiments to ensure equivalent sensitivities of the response platforms over the test period.

2.4. Experimental procedure

The test session began by placing a subject in the stabilimeter cage for a 5-min exposure to the background noise. After this acclimatization period, the rats were presented with a series of 10 stimuli (pulse alone — 120 dB, 50 ms duration), with an inter-trial interval of 20 s. The purpose of this phase was to allow within-session habituation to the startle stimulus. Thereafter, the PPI modulation of the acoustic startle was tested in two different protocols. Protocol 1 (experiments 1, 3, 4 and 5): consisted of 60 trials pseudorandomly divided into four different categories presented with an inter-trial interval of 20 s: 20 presentations of pulse alone (120 dB, 50 ms duration), 10 presentations of prepulse alone (75 dB, 3000 Hz frequency, 20 ms duration), 20 presentations of prepulse + pulse (with 50 ms interval) and 10 no stimuli trials (stabilimeter recordings obtained when no stimulus was presented) (adapted from Ross et al., 2008). Protocol 2 (experiment 2): consisted of 74 trials pseudorandomly divided into seven different categories presented with an inter-trial interval of 20 s: 20 presentations of pulse alone (120 dB, 50 ms duration), 8 presentations of each prepulse intensity alone (70,75 and 80 dB, 3000 Hz frequency, 20 ms duration) and 10 presentations of each prepulse intensity + pulse (with 50 ms interval) (adapted from Gururajan et al., 2010).

All rats were submitted to a previous PPI session without drug administration. After this session, called "matching" (Swerdlow et al., 2005; Frau et al., 2007), rats were distributed into pharmacological groups (vehicle or drug, for each experiment) matched for basal %PPI. After seven days, each rat was submitted to a test session.

2.5. Experimental design

2.5.1. Experiment 1 — comparison of basal % PPI between WR and SHR

WR and SHR (n = 9–10) were submitted to PPI test.

2.5.2. Experiment 2 — comparison of basal % PPI between WR and SHR using a protocol with three prepulse intensities

WR and SHR (n = 8–9) were submitted to PPI test using the protocol with 3 different prepulse intensities (protocol 2).

2.5.3. Experiment 3 — effects of amphetamine on % PPI of WR and SHR

WR and SHR (n = 8) were treated with vehicle (veh) or 5 mg/kg amphetamine (amph). Fifteen minutes later, the rats were submitted to the PPI test.

2.5.4. Experiment 4 — effects of typical and atypical antipsychotics on %PPI of WR and SHR

WR and SHR (n = 8) were treated with vehicle (veh), 0.1 mg/kg haloperidol (halo) or 2.5 mg/kg clozapine (clo). Thirty minutes later, the rats were submitted to the PPI test.

2.5.5. Experiment 5 — effects of carbamazepine (mood stabilizer) or metoclopramide (D_2 antagonist without antipsychotic properties) on %PPI of WR and SHR

WR and SHR (n = 9) were treated with vehicle (veh), 30 mg/kg cabamazepine (carba) or 10 mg/kg metoclopramide (meto). Thirty minutes later, the rats were submitted to the PPI test.

Based on the matching session, each animal was assigned to one drug treatment and used only once.

Doses and schedules were chosen based on our previous studies (Calzavara et al., 2009, Calzavara et al., 2011).

2.6. Statistical analysis

Mean amplitude of startle response to pulse-alone (P) and prepulse-pulse (PP + P) trials were calculated for each subject. The level of PPI in each rat was determined by expressing the prepulse + pulse startle amplitude as a percentage decrease from pulse-alone startle amplitude, according to the following formula:

$$\%PPI = 100 - [100 \times (PP/P)]$$

Using this formula, a 0% value denotes no difference between amplitude of startle response to pulse alone and to the prepulse + pulse and, consequently, no PPI. Data were analyzed by Student's test for comparisons between two groups (experiment 1), by a repeated measures two-way ANOVA (strain × prepulse intensities) followed by Paired-Samples *T* test (experiment 2), or by a two-way ANOVA (strain x drug) followed by Duncan's test (experiments 3 ,4 and 5) and . The $p<0.05$ was used as a criterion for statistical significance.

3. Results

3.1. Experiment 1 — comparison of basal %PPI between WR and SHR

Student's *T* test indicated that SHR presented a significant decrease in PPI when compared with WR [$t(17) = 3.95$; $p<0.01$] (Fig. 1).

3.2. Experiment 2 — comparison of basal % PPI between WR and SHR using a protocol with three prepulse intensities

Repeated measures two-way ANOVA showed significant effects of prepulse intensities [$F(2,30) = 4.02$; $p<0.05$] and strain [$F(1,15) = 4.82$; $p<0.05$]. SHR presented less PPI when compared to WR. Paired-samples *T* test revealed that PPI with prepulse intensities of 75 and 80 dB was significantly higher when compared to PPI with a prepulse intensity of 70 dB ($t = -2.27$ and 2.45, $p<0.05$).

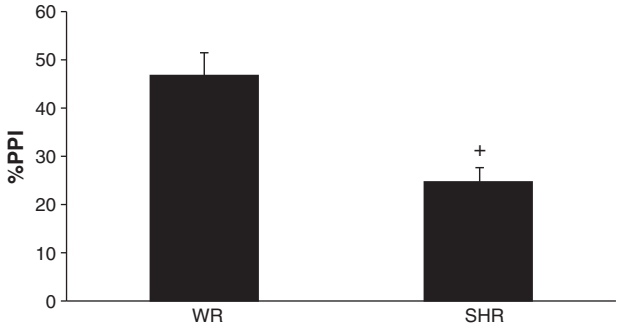

Fig. 1. % PPI of Wistar rats (WR) and SHR. + $p<0.05$ compared to WR. Student's *T* test. Data are reported as mean ± S.E.

3.3. Experiment 3 — effects of amphetamine on % PPI in WR and SHR

Two-way ANOVA detected significant strain [$F(1,28) = 7.75$; $p \leq 0.01$] and treatment [$F(1,28) = 9.11$; $p \leq 0.01$] effects. SHR presented a significant decrease in PPI when compared to WR. Amphetamine-treated animals presented a significant decrease in PPI when compared to the vehicle-treated animals (Fig. 2).

3.4. Experiment 4 — effects of typical and atypical antipsychotics on %PPI in WR and SHR

Two-way ANOVA detected significant strain [$F(1, 42) = 21.05$; $p \leq 0.01$] and treatment [$F(2, 42) = 4.42$; $p \leq 0.05$] effects. SHR presented a significant decrease in PPI when compared to WR. Post hoc analysis revealed that clozapine-treated animal showed a significant increase in PPI when compared to the vehicle-treated animals (Fig. 3).

3.5. Experiment 5 — effects of carbamazepine (mood stabilizer) and metoclopramide (D_2 antagonist without antipsychotic properties) on %PPI in WR and SHR

Two-way ANOVA detected a significant strain effect [$F(1,48) = 20.47$; $p \leq 0.01$]. SHR presented a significant decrease in PPI when compared to WR (Fig. 4).

4. Discussion

Our results demonstrate that SHR present a spontaneous deficit in PPI (experiment 1) that can be detected with different prepulse intensities (experiment 2). This deficit is similar to the deficit induced by amphetamine in Wistar rats (experiment 3). Only the atypical antipsychotic clozapine reverted this deficit (experiment 4).

Deficits in sensorimotor gating, reflected by an impairment in PPI, is presented in psychiatric disorders such as schizophrenia (Braff et al., 2001; Geyer et al., 2001; Weiss and Feldon, 2001), bipolar disorder (Perry et al., 2001) and ADHD (Hawk et al., 2003). In this sense, a pharmacological characterization of the PPI deficit presented by SHR is

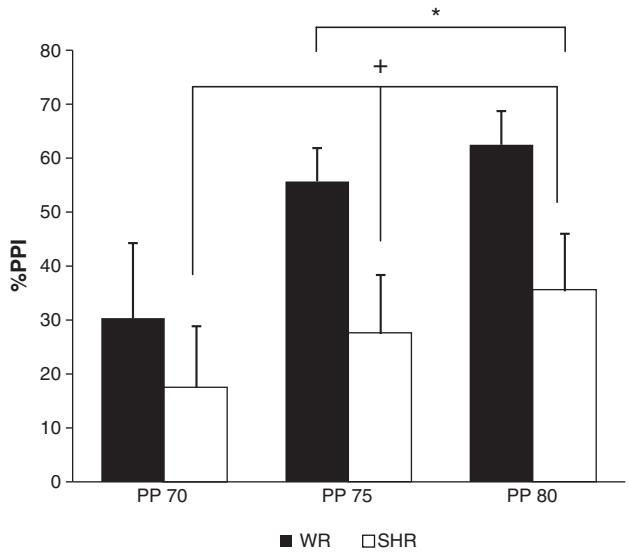

Fig. 2. % PPI of Wistar rats (WR) and SHR using three different prepulse + pulse (PP) intensities (70, 80 and 85 dB). + $p<0.05$ compared to WR. * $p<0.05$ when compared to PP 70. Repeated measures two-way analysis of variance followed by paired-samples *T* test. Data are reported as mean ± S.E.

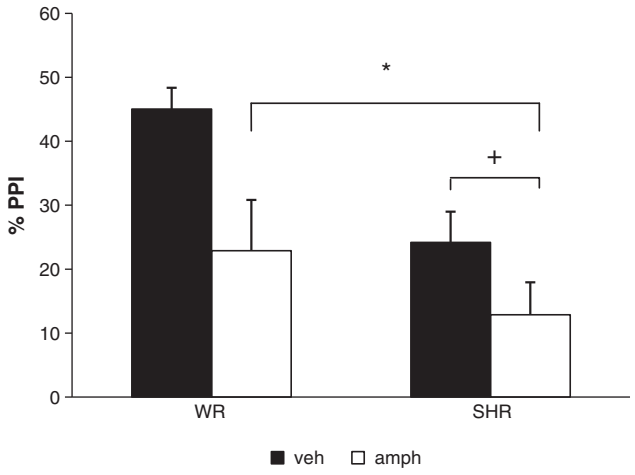

Fig. 3. % PPI of Wistar rats (WR) and SHR treated with vehicle (veh) or 5 mg/kg amphetamine (amph). * $p<0.05$ compared to vehicle-treated animals. + $p<0.05$ compared to WR. Two-way analysis of variance. Data are reported as mean ± S.E.

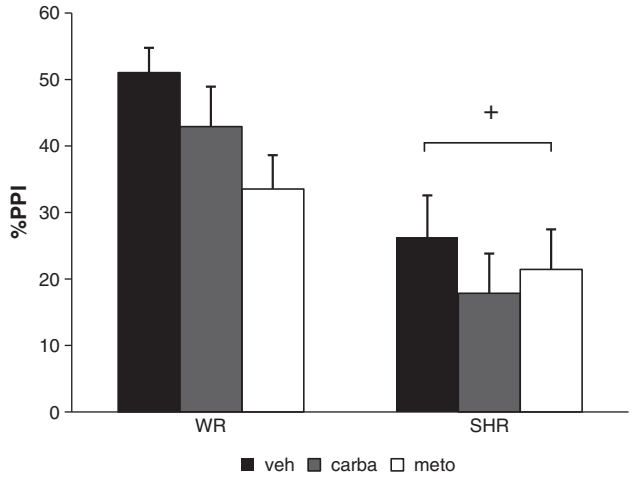

Fig. 5. %PPI of Wistar rats (WR) and SHR treated with vehicle, 30 mg/kg carbamazepine (carba) or 10 mg/kg metoclopramide (meto). + $p<0.05$ compared to WR. Two-way analysis of variance. Data are reported as mean ± S.E.

important to evaluate the potential of this strain as a model to psychiatric disorders. Considering that SHR is suggested as an ADHD model (Russell, 2007; Sagvolden and Sergeant, 1998) and that amphetamine is recommended for its treatment, we tested this drug on the PPI deficit in SHR. Amphetamine was not able to ameliorate the PPI deficit presented by SHR (Fig. 3). In accordance, some studies have also reported the absence of beneficial effects of psychostimulants on behavioral alterations presented by this strain (Bizot et al., 2007, Calzavara et al., 2009; Ferguson et al., 2007; Van den Bergh et al., 2006).

Amphetamine induced a disruption of PPI. This result corroborates previous data (Geyer et al., 2001; Zhang et al., 2000). In this respect, psychotomimetic agents, such as amphetamine, disrupt PPI in rodents (Geyer et al., 2001), mimicking the sensoriomotor gating deficit of schizophrenia patients (Ong et al., 2005). In addition, a previous work (Van den Buuse, 2004) using SHR and different control strains demonstrated that a 10 times lower dose of amphetamine is able to impair PPI in SHR (conversely to ours, in this study basal level of PPI in SHR tended to be higher than in the other strains used). Interestingly, the diminished PPI basal level in SHR is of the same magnitude than the PPI observed in amphetamine-treated WR.

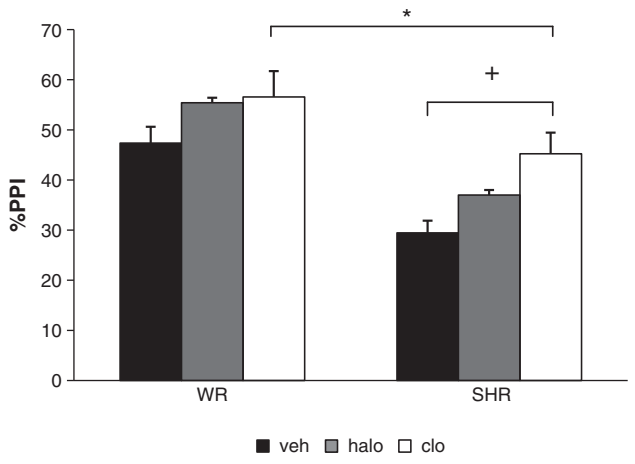

Fig. 4. % PPI of Wistar rats (WR) and SHR treated with vehicle (veh), 0.1 mg/kg haloperidol (halo) or 2.5 mg/kg clozapine (clo). * $p<0.05$ compared to vehicle-treated animals. + $p<0.05$ compared to WR. Two-way analysis of variance followed by Duncan's test. Data are reported as mean ± S.E.

The PPI deficits presented by SHR could be related to the PPI deficits presented by bipolar patients with acute psychotic mania (Perry et al., 2001). If this was true, one might expect that carbamazepine – which is beneficial to treat other symptoms of this disease – might ameliorate the deficit in PPI presented by SHR. Contrary to this possibility, this drug did not alter the deficit in PPI presented by this strain (Fig. 5). Fewer studies have reported the effects of mood stabilizers on PPI in rodents (Brody et al., 2003; Flood et al., 2009; Ong et al., 2005). Specifically related to carbamazepine, Ong et al. (2005) showed that 50 mg/kg carbamazepine prevented ketamine-induced but not amphetamine-induced disruption of PPI in C57BL/6 J mice. Another study (Flood et al., 2009) demonstrated that different doses of carbamazepine increased percent PPI in the DBA/2 mouse model of naturally low PPI. To strengthen the ineffectiveness of carbamazepine on the PPI deficit displayed by SHR it would be interesting to test a dose–response curve.

On the basis of our previous data demonstrating that SHR present deficits in contextual fear conditioning and in social interaction that are specifically reverted by antipsychotic drugs and potentiated by psychostimulants (Calzavara et al., 2009; Calzavara et al., 2011), we hypothesized that typical and atypical antipsychotics could also be beneficial for the PPI deficits exhibited by this strain. Typical and atypical antipsychotics are the conventional treatment for schizophrenia but they do not demonstrate the same beneficial effects for all classes of symptoms (Miyamoto et al., 2005). Of note, the reduction in PPI presented by SHR was significantly improved only by the atypical antipsychotic clozapine (the increase in PPI induced by clozapine is independent of the strain) (Fig. 4). Our results are in accordance with the clinical effectiveness of these drugs, particularly of atypical antisychotics, in improving PPI deficit in schizophrenia patients (Hamm et al., 2001; Kumari and Sharma, 2002; Swerdlow et al., 2006; Wynn et al., 2007). On the other hand, both typical and atypical antipsychotics attenuate PPI deficit in animal models using "proschizophrenia" manipulations (Geyer et al., 2001; Swerdlow et al., 1994, Weiss and Feldon, 2001). Hence, SHR seem to present an advantage over these other models since this strain displays a greater sensitivity to atypical antipsychotics for the PPI deficits.

Although the beneficial effect of clozapine in ameliorating PPI is in accordance with the therapeutic profile of antipsychotics in treating schizophrenia-related PPI deficits, this result could merely reflect the modulatory effect of the dopamine neurotransmission on PPI (Swerdlow et al., 2001). In order to verify this hypothesis, we evaluated the effects of metoclopramide, a D_2 antagonist without antipsychotic activity. Corroborating the association of this deficit with schizophrenia-related sensorimotor gating impairment, the PPI

deficit in SHR was not reverted by this drug (although only one dose was tested) (Fig. 5).

5. Conclusion

The spontaneous PPI deficit presented by SHR was specifically reverted by the atypical antipsychotic clozapine. In this sense, the attenuation of PPI deficits by antipsychotics is a hallmark of schizophrenia animal models. Therefore, the beneficial effects of clozapine on the PPI deficit presented by SHR add to our previous work (Calzavara et al., 2009 and 2011) extending the usefulness of this strain also to study sensorimotor gating abnormalities associated with schizophrenia.

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