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Effects of Topiramate on the Prepulse Inhibition of the Acoustic Startle in Rats

Roberto Frau[1], Marco Orrù[2], Mauro Fà[1], Alberto Casti[1], Mario Manunta[2], Nicola Fais[2], Giampaolo Mereu[2], Gianluigi Gessa[1] and Marco Bortolato*[,1,3]

[1]Department of Neuroscience, 'Bernard B. Brodie', University of Cagliari, Cagliari, Italy; [2]Department of Experimental Biology, University of Cagliari, Cagliari, Italy; [3]Department of Psychiatry and Human Behavior, University of California, Irvine, CA, USA

The anticonvulsant topiramate (TPM) has been recently proposed as a novel adjuvant therapy for bipolar disorder and schizophrenia, yet its efficacy remains controversial. As both disorders are characterized by gating deficits, we tested the effects of TPM on the behavioral paradigm of prepulse inhibition (PPI) of the acoustic startle response, a validated animal model of sensorimotor gating. TPM (10, 18, 32, 58, 100 mg/kg, intraperitoneal, i.p.) enhanced PPI in rats in a dose-dependent fashion, prevented the PPI reduction mediated by the dopaminergic agonist apomorphine (0.25 mg/kg, subcutaneous, s.c.) and potentiated the effects of the antipsychotic drugs haloperidol (0.05, 0.1 mg/kg, i.p.) and clozapine (2.5, 5 mg/kg, i.p.). Conversely, TPM elicited no significant effect on the PPI disruption mediated by the NMDA receptor antagonist dizocilpine (0.05, 0.1 mg/kg, s.c.) and surprisingly antagonized the attenuation of dizocilpine-induced PPI disruption mediated by clozapine (5 mg/kg, i.p.). Our results suggest that TPM may exert diverse actions on the neural substrates of sensorimotor gating. While the pharmacological mechanisms of such effects are still elusive, our findings might contribute to shed light on some controversies on the therapeutic action of TPM, and point to this drug as a putative novel adjuvant therapy for some clusters of gating disturbances.

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INTRODUCTION

Topiramate (TPM, 2,3:4,5-bis-*O*-1-methylethylidene-beta-D-fructopyranose sulfate) is a novel therapeutic agent, currently indicated as adjunctive treatment for refractory partial-onset or primary generalized tonic-clonic seizures, as well as for migraine prophylaxis (Shank *et al*, 2000; Silberstein *et al*, 2005). Although its mechanisms of action have not been fully elucidated, TPM is known to enhance the activity of γ-aminobutyric acid (GABA) through interaction with $GABA_A$ receptors, as well as to block voltage-dependent sodium channels and kainate/[alpha]-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) glutamate receptors (Schneiderman, 1998). Emerging evidence indicates that TPM might offer promising applications for the therapy of other neurological conditions, such as neuropathic pain and essential tremor (Chong and Libretto, 2003; Connor, 2002), as well as several psychiatric disorders, such as bipolar disorder (Calabrese *et al*, 2001; Grunze *et al*, 2001), schizoaffective disorder (Deutsch *et al*, 2003), posttraumatic disorder (Berlant and Van Kammen, 2002), Tourette's syndrome (Abuzzahab and Brown, 2001) and some clusters of schizophrenia (Drapalski *et al*, 2001). The therapeutic potential of TPM for these disorders, however, is disputed on account of contrasting findings (Arnone, 2005; Millson *et al*, 2002) and in view of its numerous cognitive and affective side effects, such as depression, hallucinosis and cognitive deterioration (Matthews and Miller, 2001). Thus, TPM has been alternately described to have therapeutic efficacy against negative symptoms in psychotic patients (Drapalski *et al*, 2001) and to produce paranoid delusions, auditory hallucinations, depersonalization, suicidal thoughts, aggressive behavior and severe mood swings (Khan *et al*, 1999; Stella *et al*, 2002; Mula *et al*, 2003). Similarly, TPM has also been reported to either exacerbate (Kaplan, 2005) or treat manic disorders (Chengappa *et al*, 1999). In spite of their distinct nosographic profiles and pathophysiological heterogeneity, both schizophrenia and bipolar disorder—like most of the aforementioned psychiatric disorders putatively treated by TPM—display a general alteration in sensorimotor gating (for a review, see Braff *et al*, 2001), suggesting that TPM might actually modulate perceptual functions. Nevertheless, to the best of our knowledge, this hypothesis has not been

*Correspondence: Dr M Bortolato, Department of Psychiatry and Human Behavior, 3216, Gillespie Neuroscience Research Facility, University of California, Irvine, CA 92697-4260, USA, Tel: + 1 949 824 7080, Fax: + 1 949 824 6305, E-mail: bortolam@uci.edu

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tested to date. The aim of the present study was the elucidation of the effects of TPM on the behavioral paradigm of prepulse inhibition (PPI) of the acoustic startle response (ASR), a highly dependable model for the evaluation of sensorimotor gating (Swerdlow *et al*, 2001). The PPI consists in the reduction of the startle reflex that occurs when the eliciting stimulus is immediately preceded by a prepulse, a weak, nonstartling prestimulus (Graham, 1975). This physiological phenomenon can be typically disrupted in animals via several pharmacological treatments, mainly NMDA receptor antagonists, such as phencyclidine and dizocilpine, and dopaminergic agonists, such as amphetamine and apomorphine (for a review, see Geyer *et al*, 2001). It has also been shown that typical and atypical antipsychotics are effective in preventing PPI disruption mediated by dopaminergic agonists (Mansbach *et al*, 1988; Swerdlow *et al*, 1991); moreover, atypical, but not typical antipsychotics antagonize the PPI disruption caused by NMDA receptor antagonists (Geyer *et al*, 1990; Bakshi *et al*, 1994). Specifically, we evaluated the effects of TPM, both alone and in cotreatment with haloperidol and clozapine, against the disruption of PPI induced by apomorphine and dizocilpine.

MATERIALS AND METHODS

Animals

Six hundred twenty-six male Sprague–Dawley albino rats (Harlan, Italy) weighing between 200 and 300 g served as subjects in the present study. Rats were housed four per cage in the animal care quarters, maintained at a temperature of $22 \pm 2^{\circ}$C on a reversed 12-h light–dark cycle (lights went off at 0700 and on at 1900). Food and water were available *ad libitum*, and each rat was handled for 5 min on each of the 5 days prior to experiment to minimize stress effects. All experimental procedures were approved by the local ethical committee and carried out in strict accordance with the Economic Community (EC) guidelines for care and use of experimental animals (86/609/European EC).

Drugs and Chemicals

The following drugs were used: TPM, apomorphine hydrocloride, dizocilpine maleate, haloperidol, and clozapine. All drugs were purchased from Sigma Aldrich, Italy. Apomorphine was dissolved in 0.9% saline with 0.1 mg/ml ascorbic acid. TPM and dizocilpine were dissolved in 0.9% saline. Haloperidol was dissolved in 10% acetic acid buffered with sodium hydroxide (NaOH) and diluted with saline, while clozapine was dissolved in a single drop of 1 N chloridric acid (HCl) and diluted with saline. The pH was adjusted to seven using sodium bicarbonate ($NaHCO_3$). All drugs were weighed out as salts and administered in an injection volume of 1 ml/kg.

Apparatus

The apparatus for the detection of the startle reflexes (Med Associates, St Albans, Vermont) consisted of four standard cages placed in sound-attenuated chambers with fan ventilation. The cage was a Plexiglas cylinder of 9 cm diameter, mounted on a piezoelectric accelerometric platform connected to an analogue-digital converter. Background noise and acoustic bursts were conveyed by two separate speakers, placed at 7 cm beside the startle cage so as to produce a variation of sound within 1 dB across it. Both speakers and startle cages were connected to a main personal computer (PC), which detected and analyzed all chamber variables by means of custom software. Acoustic stimuli were monitored and balanced before each testing session through a digital sound level meter (Extech Instruments, Waltham, MA, USA), while the mechanical response of each cage was set and equalized in all chambers via a 10-Hz spinner calibrator provided by Med Associates.

Procedure

At 3 days before the experiment, all rats went through a brief baseline startle session. Rats were exposed to a background noise of 70 dB, and after an acclimatization period of 5 min, they were presented with a randomized sequence of 12 40 ms bursts of 115 dB, interposed with three trials in which a 82-dB prestimulus preceded the same pulse by 100 ms. Rats exhibiting baseline very high or very low startle values (more than two SD above or below group mean values) were excluded from the study. Subsequently, treatment groups were established so that the average startle response and percent PPI of each group were equivalent in all groups. On the testing day, each rat was placed in a cage for a 5-min acclimatization period with a 70-dB white noise background, which continued for the remainder of the session. Each session consisted of three consecutive sequences of trials (periods). Unlike the first and the third periods, during which rats were presented with only five pulse-alone trials of 115 dB, the second period consisted of a pseudorandom sequence of 50 trials, including 12 pulse-alone trials; 30 trials of pulse preceded by 73-dB, 76-dB, or 82-dB prepulses (10 for each level of prepulse loudness); and eight no-stimulus trials, where only the background noise was delivered. Intertrial intervals (ITI) were selected randomly between 10 and 15 s. The startle session lasted about 30 min.

Experiment Description

This study consisted of seven experiments. In the first experiment ($n = 66$; 6 groups of animals), we evaluated the intrinsic effect of TPM on PPI by treating animals with either 0.9% saline or TPM (10, 18, 32, 58, 100, intraperitoneal (i.p.)). The second experiment ($n = 88$; 8 groups of animals) was carried out to verify whether TPM (18, 32, 58 mg/kg, i.p.) prevents the PPI deficit induced by apomorphine (0.25 mg/kg, subcutaneous (s.c.)). Following the discovery that TPM reduces PPI disruption mediated by apomorphine, in the third and the fourth experiment ($n = 96$; 12 groups of rats for each experiment) we tested whether this effect might be synergistic with the antipsychotic-like properties of haloperidol (0.05, 0.1 mg/kg i.p.) and clozapine (2.5, 5 mg/kg i.p.) to prevent apomorphine-mediated PPI disruption. The fifth experiment ($n = 88$, eight groups) was aimed at the evaluation of the action of TPM against dizocilpine-mediated PPI deficit. Subsequently, we

tested whether the combination of TPM (32 mg/kg, i.p.) and haloperidol (0.1, 0.5 mg/kg, i.p.) was effective in reversing the PPI disruption mediated by dizocilpine (0.1 mg/kg, s.c.) ($n = 96$; 12 groups of animals). Finally, the seventh experiment ($n = 96$ rats, divided into 12 treatment groups), was performed to test the ability of the combination of TPM (32 mg/kg, i.p.) and clozapine (2.5, 5 mg/kg, i.p.) to antagonize PPI deficits induced by dizocilpine (0.1 mg/kg, s.c.), respectively. All substances were administered at a convenient time interval before experimental testing, compatible with their pharmacokinetic characteristics, so as to elicit their effects during the startle session. Table 1 presents a synopsis of the whole study, detailing the time intervals for each treatment in all the experiments.

Data Analysis

For each animal, the mean startle amplitudes for the first and the second halves of the second period of the session (blocks, six pulse-alone trials each) were analyzed with a two-way or three-way analysis of variance (ANOVA), with pretreatment (where present) and treatment as between-subjects factors and blocks as repeated measures. The percent PPI was calculated with the following formula: 100−((mean startle amplitude for prepulse + pulse trials/mean startle amplitude for pulse-alone trials) × 100) and analyzed in multifactor ANOVAs (with specific design and comparisons noted below for each experiment) with the different combinations of injections for pretreatment and treatment as between-subjects factors and trial types as repeated measures. *Post hoc* analyses were performed using Tukey's test. Alpha was set at 0.05.

RESULTS

Throughout the study, no-stimulus trials data were found negligible in comparison with other startle values and nor were they affected by any drug treatment; therefore, they will not be presented here.

Effects of TPM

The first experiment was aimed at assessing the effects of TPM (TPM, 10, 18, 32, 58, 100 mg/kg, i.p.) on startle reflex and PPI, in comparison with saline. Startle magnitudes were evaluated using a two-way, repeated-measure ANOVA, with treatments and blocks as variables. As shown in Table 2, statistical analysis assessed that the dose of 10 mg/kg (i.p.) produced a significant reduction in startle magnitude [$F(5,60) = 13.58$; $p < 0.001$, ANOVA; $p < 0.001$, Tukey's test]. Moreover, ANOVA revealed a habituation effect in startle amplitude, expressed as a difference in ASR between the two blocks of each session [$F(1,60) = 186.40$; $p < 0.001$]. Finally, no interaction effect was found [$F(5,60) = 1.77$; not significant (NS)]. The subsequent statistical analysis on PPI values, performed via a two-way ANOVA—with treatments and prepulse levels—detected that TPM is significantly able to enhance PPI values [$F(5,60) = 78.13$; $p < 0.001$]. *Post hoc* analysis confirmed that the doses of 32, 58 and 100 mg/kg (i.p.) are able to enhance PPI levels in comparison with controls ($p < 0.001$ 32 and 58 mg/kg, $p < 0.01$ 100 mg/kg, in comparison with saline, Tukey's test). Interestingly, the doses of 10, 18, and 100 mg/kg i.p. appeared unable to significantly affect %PPI, thus outlining an inverse U-shaped effect of TPM on PPI (Figure 1). Finally, ANOVA showed a significant effect for prepulse intensity [$F(2,120) = 217.02$; $p < 0.001$].

Effects of TPM Pretreatment *vs* Apomorphine

In the second experiment, we tested the effect of a TPM pretreatment (32, 58 mg/kg, i.p.) on the PPI disruption mediated by apomorphine (APO, 0.25 mg/kg, s.c.). Startle amplitudes were compared by a three-way ANOVA, with pretreatment and treatment as independent variables and blocks as repeated factors. In keeping with previous findings by our group (Bortolato *et al*, 2004), apomorphine produced a slight, yet significant enhancement of startle amplitude in comparison with controls [$F(1,80) = 21.31$, $p < 0.001$]. However, ANOVA was unable to detect any significant effect for either pretreatment [$F(3,80) = 1.30$, NS] or the interaction pretreatment × treatment × blocks [$F(3,80) = 0.91$, NS], confirming the paucity of effects exerted by TPM—in the range of dosages tested here—on ASR. Finally, a habituation effect was again revealed by the comparison between session blocks [$F(1,80) = 258.03$, $p < 0.001$] (Table 2). %PPI analysis, conducted by a second three-way, repeated-measure ANOVA, showed that apomorphine produced a dramatic reduction in PPI, as expected [$F(1,80) = 106.68$, $p < 0.001$]. Interestingly, ANOVA also revealed significant effects for the pretreatment factor (TPM *vs* SAL) [$F(3,80) = 103.71$, $p < 0.001$] and

Table 1 Prospectus of the Timelines of the Experiments of the Whole Study

	−60′	−45′	−40′	−5′	−1′	0′→5′	5′→30′
Experiment 1		TPM/SAL				HABITUATION	SESSION
Experiment 2		TPM/SAL			APO/SAL	HABITUATION	SESSION
Experiment 3	HAL/SAL	TPM/SAL			APO/SAL	HABITUATION	SESSION
Experiment 4		TPM/SAL	CLO/SAL		APO/SAL	HABITUATION	SESSION
Experiment 5		TPM/SAL		DIZ/SAL		HABITUATION	SESSION
Experiment 6	HAL/SAL	TPM/SAL		DIZ/SAL		HABITUATION	SESSION
Experiment 7		TPM/SAL	CLO/SAL	DIZ/SAL		HABITUATION	SESSION

SAL, saline; TPM, TPM; HAL, haloperidol; CLO, clozapine; DIZ, dizocilpine; APO, apomorphine.

Table 2 Mean Startle Amplitudes of Treatment Groups in all Experiments

Groups	Mean SA	First block	Second block
Experiment 1			
SAL	591.23±25.17	600.12±25.54	582.34±24.86
TPM 10	612.27±17.28	620.17±17.05	604.38±17.6
TPM 18	614.96±17.8	622.36±17.66	607.57±18.06
TPM 32	648.08±22.55	656.36±23	639.8±22.2
TPM 58	551.07±16.37	558.2±15.7	543.94±17.1
TPM 100	441.9±18.66**	445.86±19.33	437.94±18.03
Experiment 2			
SAL-SAL	622.99±20.79	630.23±20.79	615.75±20.9
SAL-APO	661.35±25.69*	669.48±26.2	653.23±25.24
TPM 18-SAL	610.56±20.75	617.78±20.77	603.34±20.75
TPM 18-APO	645.22±18.16*	650.87±17.51	639.57±18.85
TPM 32-SAL	593.74±22.61	599.4±22.2	588.08±23.07
TPM 32-APO	696.8±22.22*	704.77±22.81	688.83±21.74
TPM 58-SAL	616.31±21.75	624.54±21.97	608.08±21.64
TPM 58-APO	723.56±20.9*	733.95±21.41	713.16±20.52
Experiment 3			
SAL-SAL	627.57±22.27	632.08±21.77	623.06±22.8
SAL-DIZ	648.42±20.81	655.64±21.01	641.19±20.7
TPM 18-SAL	590.37±27.15	595.99±28.02	584.76±26.32
TPM 18-DIZ	595.97±20.28	604.68±20.64	587.26±19.96
TPM 32-SAL	621.66±21.81	631.72±22.61	611.6±21.08
TPM 32-DIZ	652.6±21.97	658.1±22.85	647.09±21.17
TPM 58-SAL	623.22±21.91	630.22±21.44	616.21±22.43
TPM 58-DIZ	605.55±15.56	611.29±15.02	599.81±16.19
Experiment 4			
SAL-SAL-SAL	576.58±19.99	579.59±20.15	573.57±19.85
SAL-SAL-APO	736.82±15.15**	746.78±16.8	726.86±13.53
SAL-HAL 0.05-SAL	623.89±17.69	633.95±17.6	613.84±17.85
SAL-HAL 0.05-APO	687.9±14.2	696.26±14.08	679.53±14.53
SAL-HAL 0.1-SAL	547.42±17.77*	554.59±17.97	540.25±17.61
SAL-HAL 0.1-APO	574.17±17.72	581.93±17.95	566.41±17.56
TPM 18-SAL-SAL	607.97±19.08	616.83±19.94	599.12±18.25
TPM 18-SAL-APO	685.35±29.96	694.97±30.49	675.74±29.45
TPM 18-HAL 0.05-SAL	607.39±17.2	614.6±16.98	600.19±17.55
TPM 18-HAL 0.05-APO	667.5±21.7	674.62±21.22	660.37±22.21
TPM 18-HAL 0.1-SAL	515.41±12.55**	521.42±12.62	509.39±12.59
TPM 18-HAL 0.1-APO	568.55±23.5	577.49±24.22	559.6±22.86
Experiment 5			
SAL-SAL-SAL	592.86±12.87	597.07±13.36	588.66±12.48
SAL-SAL-APO	714.95±14.68**	725.07±14.96	704.83±14.54
SAL-CLO 2.5-SAL	607.94±20.46	616.94±20.54	598.94±20.43
SAL-CLO 2.5-APO	645.23±21.02	651.14±21.64	639.32±20.44
SAL-CLO 5-SAL	520.6±15.29*	526.72±15.24	514.48±15.41
SAL-CLO 5-APO	611.69±29.25	619.42±30.63	603.96±27.88
TPM 18-SAL-SAL	565.33±24.57	574.67±24.77	556±24.41
TPM 18-SAL-APO	770.11±25.28**	778.81±26.13	761.41±24.54

Table 2 Continued

Groups	Mean SA	First block	Second block
TPM 18-CLO 2.5-SAL	665.27 ± 13.54	673.66 ± 13.54	656.87 ± 13.63
TPM 18-CLO 2.5-APO	636.2 ± 17.93	641.34 ± 18.07	631.05 ± 17.84
TPM 18-CLO 5-SAL	526.78 ± 20.84*	534.39 ± 20.89	519.17 ± 20.84
TPM 18-CLO 5-APO	601.9 ± 28.23	608.44 ± 28.89	595.37 ± 27.6
Experiment 6			
SAL-SAL-SAL	602.1 ± 18.03	609.05 ± 18.01	595.15 ± 18.17
SAL-SAL-DIZ	616.18 ± 19.01	626.62 ± 19.49	605.74 ± 18.59
SAL-HAL 0.1-SAL	588.65 ± 21.33	594.62 ± 21.81	582.68 ± 20.91
SAL-HAL 0.05-DIZ	641.98 ± 25.65	646.62 ± 25.68	637.34 ± 25.66
SAL-HAL 0.1-SAL	528.54 ± 19.74*	537.69 ± 20.4	519.39 ± 19.09
SAL-HAL 0.1-DIZ	536.92 ± 21.73*	543.9 ± 21.57	529.94 ± 21.98
TPM 18-SAL-SAL	567.24 ± 20.78	573.15 ± 21.05	561.34 ± 20.59
TPM 18-SAL-DIZ	641.5 ± 17.31	648.24 ± 17.22	634.75 ± 17.46
TPM 18-HAL 0.05-SAL	605.75 ± 22.1	611.34 ± 22.1	600.15 ± 22.16
TPM 18-HAL 0.05-DIZ	632.67 ± 29.03	642.38 ± 29.13	622.96 ± 29
TPM 18-HAL 0.1-SAL	540.48 ± 16.8*	548.03 ± 17.36	532.92 ± 16.28
TPM 18-HAL 0.1-DIZ	525.25 ± 14.57*	531.45 ± 14.93	519.05 ± 14.24
Experiment 7			
SAL-SAL-SAL	570.88 ± 20.89	576.99 ± 21.08	564.77 ± 20.73
SAL-SAL-DIZ	584.45 ± 26.18	592.2 ± 25.9	576.71 ± 26.53
SAL-CLO 5-SAL	552.28 ± 17.12	557.7 ± 17.25	546.86 ± 17.03
SAL-CLO 2.5-DIZ	607.66 ± 19.97	614.91 ± 21.07	600.41 ± 19.01
SAL-CLO 5-SAL	491.38 ± 16.77**	497.24 ± 17.68	485.52 ± 15.88
SAL-CLO 5-DIZ	474.3 ± 23.75**	480.51 ± 24	468.09 ± 23.59
TPM 18-SAL-SAL	587.01 ± 19.66	594.5 ± 20.03	579.53 ± 19.38
TPM 18-SAL-DIZ	576.2 ± 24.88	584.16 ± 25.74	568.23 ± 24.07
TPM 18-CLO 2.5-SAL	560.31 ± 13.26	566.71 ± 13.4	553.9 ± 13.28
TPM 18-CLO 2.5-DIZ	593.9 ± 17.74	601.97 ± 18.46	595.82 ± 17.12
TPM 18-CLO 5-SAL	530.54 ± 13.71*	536.01 ± 14.23	525.08 ± 13.28
TPM 18-CLO 5-DIZ	479.21 ± 16.2**	486.26 ± 16.42	472.15 ± 16.04

Values represent mean ± SEM for each treatment. All doses are given in mg/kg. Mean SA, mean startle amplitude for the whole trial sequence; 1st Block, mean startle amplitude for the first half of the session; 2nd Block, mean startle amplitude for the second half of the session; SAL, saline; TPM, TPM; HAL, haloperidol; CLO, clozapine; DIZ, dizocilpine; APO, apomorphine. For further details, see text.
*$P<0.05$; **$P<0.01$ in comparison to saline-treated groups.

the interaction pretreatment × treatment [$F(3,80) = 42.81$, $p<0.001$]. As shown in Figure 2, *post hoc* comparisons revealed that animals treated with TPM + saline exhibited an increased %PPI in comparison with the rats subjected to a double saline injection ($p<0.01$ for each TPM dose, Tukey). Additionally, TPM pretreatment significantly reduced apomorphine-mediated PPI disruption at both doses (TPM + APO *vs* SAL + APO: $p<0.01$ for both TPM doses, Tukey). Analyses of the differences between startle magnitudes on pulse-alone and prepulse + pulse trials (ΔPPI, see Bortolato *et al*, 2004) also confirmed that the effect of TPM in restoring PPI is not reflective of changes in startle magnitude (data not shown). However, the comparison between TPM + SAL and TPM + APO groups detected no significant difference in %PPI. Finally, ANOVA revealed also a significant effect between prepulse intensities [$F(2,160) = 81.51$ $p<0.001$], but not for the interactions between prepulse levels and treatments [$F(6,160) = 1.26$, NS].

Effects of TPM in Combination with Haloperidol *vs* Apomorphine

Following the discovery that TPM can reduce the PPI-disruptive effects of apomorphine, we addressed the third experiment to the assessment of the ability of TPM (18 mg/kg, i.p.) to potentiate the PPI effects of haloperidol (HAL, 0.05, 0.1 mg/kg, i.p.). Startle amplitudes were analyzed by a four-way ANOVA, with the three series of treatments as independent variables and blocks as repeated

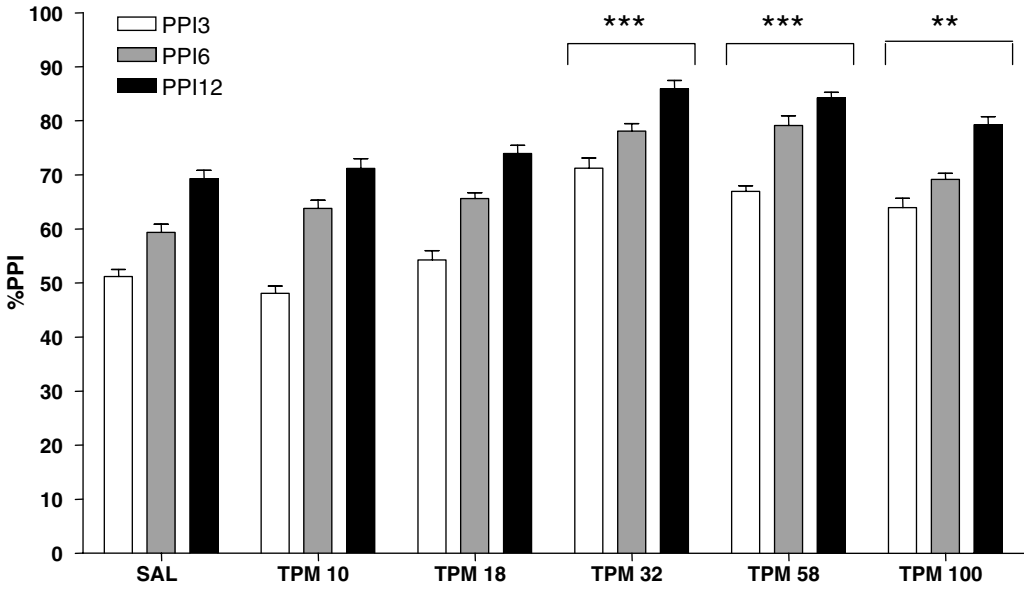

Figure 1 Effect of TPM on PPI parameters at different prepulse levels, in comparison with saline group. All TPM doses are given in mg/kg. Values represent mean ± SEM for each treatment. Prepulses are indicated by the intensity corresponding to decibels above background noise. SAL, saline; TPM, TPM. ***$p<0.001$, **$p<0.01$ compared to SAL treatment group. For further details, see text.

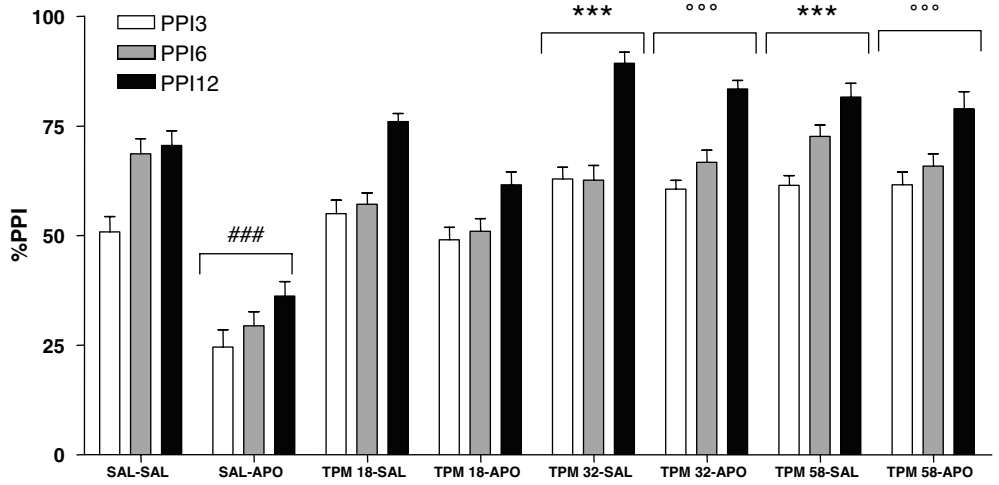

Figure 2 Effect of TPM pretreatment on the PPI disruption mediated by apomorphine. All TPM and apomorphine doses are given in mg/kg. Values represent mean ± SEM for each treatment. Prepulses are indicated by the intensity corresponding to decibels above background noise. SAL, saline; TPM, TPM; APO, apomorphine; ###$p<0.001$, ***$p<0.001$ compared to SAL + SAL group; °°°$p<0.01$ compared to SAL + APO group. For further details, see text.

measures. Statistical analyses confirmed that apomorphine significantly increased startle amplitude [$F(1,84)=29.44$, $p<0.001$] and haloperidol reduced it [$F(2,84)=25.25$, $p<0.001$, ANOVA; $p<0.01$ for the comparison between 0.1 mg/kg and saline, Tukey's test]. Finally, ANOVA showed a significant effect for blocks, again confirming a time-dependent reduction in startle reactivity throughout the session, irrespective of treatments [$F(1,84)=319.23$, $p<0.001$]. Following the analysis on startle reflex, a further four-way ANOVA, with the same independent variables and PPI levels as repeated measures, served to test PPI values. Apomorphine significantly reduced %PPI in comparison with vehicle amplitude [$F(1,84)=116.62$, $p<0.001$]. ANOVA also established that both TPM [$F(1,84)=37.44$, $p<0.001$] and haloperidol [$F(2,84)=47.69$, $p<0.001$] significantly increase PPI. *Post hoc* comparisons assessed that haloperidol significantly reduced %PPI at both doses ($p<0.01$, Tukey). A significant effect was also found for prepulse levels [$F(1,84)=79.03$, $p<0.001$]. Interestingly, ANOVA also detected a significant interaction between the three series of pretreatments [$F(2,84)=5.62$, $p<0.01$]. As shown in Figure 3, Tukey's test detected that the combination between TPM (18 mg/kg, i.p.) and haloperidol (0.05 mg/kg) produced a significant effect against apomorphine-mediated PPI disruption in comparison to the cotreatment of saline and haloperidol ($p<0.01$), thus

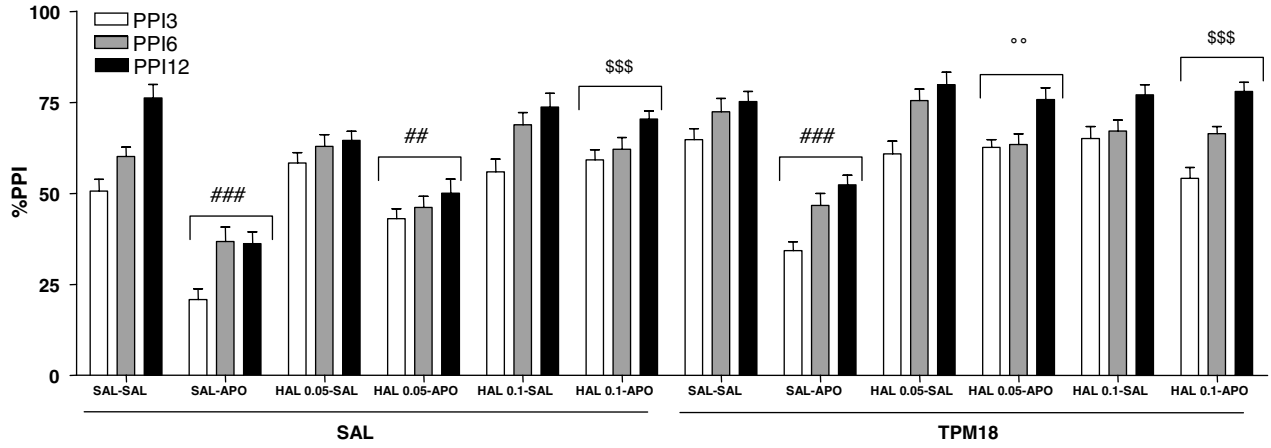

Figure 3 Antagonism of the apomorphine-induced deficit in PPI by the combination TPM + haloperidol. All doses are given in mg/kg. Values represent mean ± SEM for each treatment. Prepulses are indicated by the intensity corresponding to decibels above background noise. SAL, saline; TPM, TPM; APO, apomorphine; HAL, haloperidol. $^{###}p<0.001$, $^{##}p<0.01$ compared to SAL + SAL subgroup in both SAL and TPM pretreated groups; $^{\$\$\$}p<0.001$ compared to SAL + APO subgroup in both SAL and TPM pretreated groups; $^{\circ\circ}p<0.01$ compared to SAL + HAL + APO subgroup in TPM pretreated group. For further details, see text.

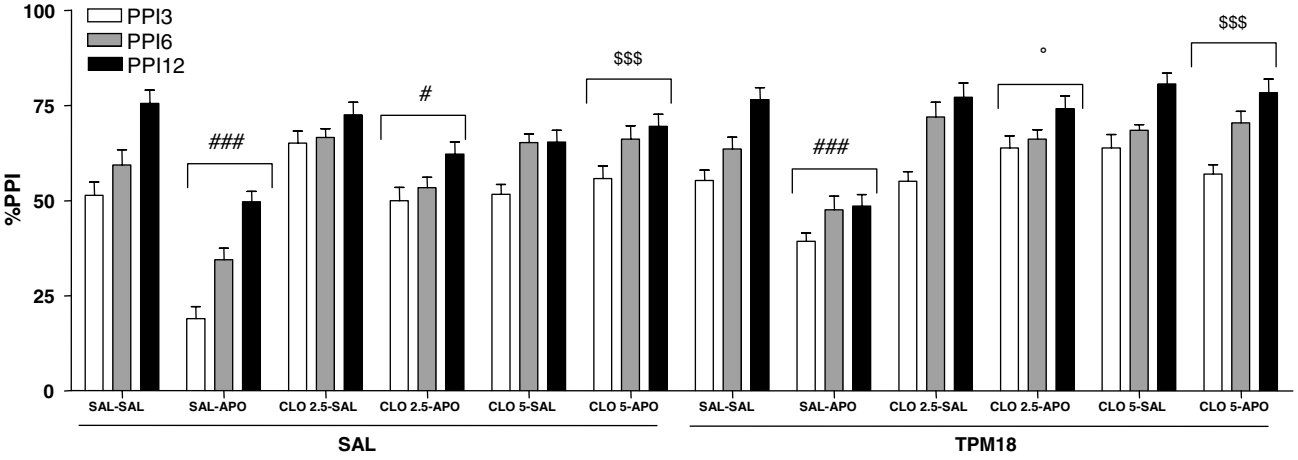

Figure 4 Antagonism of the apomorphine-induced deficit in PPI by the combination TPM + clozapine. All doses are given in mg/kg. Values represent mean ± SEM for each treatment. Prepulses are indicated by the intensity corresponding to decibels above background noise. SAL, saline; TPM, TPM; APO, apomorphine; CLO, clozapine. $^{###}p<0.001$, compared to SAL + SAL subgroup in the respective pretreatment group; $^{\#}p<0.05$ compared to CLO 2.5 + SAL subgroup in the SAL pretreatment group; $^{\$\$\$}p<0.01$ compared to SAL + APO subgroup in the SAL pretreatment group; $^{\circ}p<0.05$, compared to CLO 2.5 + APO subgroup in the SAL pretreatment group. For further details, see text.

showing that TPM was able to potentiate the antipsychotic-like effect of subthreshold dose of haloperidol. Parallel statistical analyses on ΔPPI confirmed that the restoration of PPI mediated by the combination of TPM and haloperidol is dissociated from effects on startle magnitude (data not shown).

Effects of TPM in Combination with Clozapine *vs* Apomorphine

The fourth experiment paralleled the previous one in evaluating the ability of TPM (18 mg/kg, i.p.) to potentiate the ability of clozapine (CLO, 2.5, 5 mg/kg, i.p.), in reversing the PPI disruption induced by apomorphine (0.25 mg/kg, s.c.). Startle amplitudes were analyzed by a four-way ANOVA with treatments as independent variables and blocks as repeated measures. Again, while apomorphine significantly increased startle amplitude [$F(1,84)=40.49$, $p<0.01$], the higher dose of clozapine produced a decrease of the same parameter [$F(2,84)=21.95$, $p<0.01$, ANOVA; $p<0.01$ for comparison CLO 5 *vs* SAL, Tukey's test]. Finally, ANOVA showed a significant habituation effect in the comparison between the two blocks of trials [$F(1,84)=257.73$, $p<0.001$]. Further ANOVAs, with the same independent variables and with PPI levels as repeated measures, served to test PPI values. ANOVA revealed either significant effects for each treatment (TPM *vs* saline: [$F(1,84)=57.92$, $p<0.01$]; clozapine *vs* saline: [$F(2,84)=53.86$, $p<0.01$]; apomorphine *vs* saline: [$F(1,84)=68.89$, $p<0.01$]. A significant difference between prepulse levels was also found [$F(2,168)=56.54$, $p<0.001$]. Symmetrically to the previous experiment, ANOVA also found a significant

interaction between the three series of treatments [$F(2,84) = 3.80$, $p < 0.05$]. *Post hoc* analysis assessed that TPM significantly magnified the antipsychotic-like effect of the 2.5 mg/kg dose of clozapine ($p < 0.05$. Figure 4). Comparisons between values of startle magnitude confirmed that such effect did not depend on the actions on startle magnitude (data not shown).

Effects of TPM Pretreatment *vs* Dizocilpine

The fifth experiment was performed to verify whether TPM (32, 58 mg/kg, i.p.) prevents dizocilpine (DIZ)-mediated PPI disruption. Startle amplitudes were evaluated with the same design as in the second experiment. ANOVA did not detect any significant effect, with the exception of a clear-cut habituation effect, as verified by the comparison between blocks [$F(1,80) = 212.12$, $p < 0.001$]. A second three-way ANOVA was used to analyze PPI values. Dizocilpine produced a significant disruption of PPI [$F(1,80) = 2031.08$, $p < 0.0001$]; however, no significant effect was found for the interaction pretreatment × treatment. Finally, a significant difference in prepulse levels was assessed [$F(2, 160) = 19.26$, $p < 0.01$] (Figure 5).

Effects of TPM in Combination with Haloperidol *vs* Dizocilpine

The sixth experiment evaluated the ability of the combination of TPM (32 mg/kg, i.p.) and haloperidol (0.1, 0.5 mg/kg, i.p.) in reversing the PPI disruption induced by dizocilpine (0.1 mg/kg, s.c.). Startle amplitudes were analyzed by a four-way ANOVA with treatments as independent variables and blocks as repeated measures. ANOVA showed only haloperidol was able to significantly blunt startle at both doses [$F(2,84) = 13.80$, $p < 0.001$, ANOVA; $p < 0.01$ for both doses in comparison with saline, Tukey's test]. Besides, the comparison between trial blocks assessed a time-dependent attenuation in startle amplitude ($F(1,84) = 321.09$, $p < 0.001$, Figure 1). A further ANOVA, with the same independent variables and with PPI levels as repeated measures, served to test PPI values. ANOVA only revealed a significant effects for treatment—[DIZ *vs* SAL: $F(1,84) = 1605.70$, $p < 0.0001$]. A significant difference between prepulse levels was also found [$F(2,168) = 57.28$, $p < 0.001$] (Figure 6).

Effects of TPM in Combination with Clozapine *vs* Dizocilpine

The last experiment evaluated the ability of TPM (32 mg/kg, i.p.) to interact with clozapine (2.5, 5 mg/kg i.p.), in reversing the PPI disruption induced by dizocilpine (0.25 mg/kg, s.c.). Startle amplitudes were analyzed by a four-way ANOVA with treatments as independent variables and blocks as repeated measures. ANOVA showed that clozapine was able to significantly attenuate startle amplitude [$F(2,84) = 21.94$, $p < 0.001$]. ANOVA also showed a significant effect for blocks [$F(1,84) = 227.48$, $p < 0.001$]. A subsequent analysis of variance was conducted, with the same independent variables and with PPI levels as repeated measures, served to test PPI values for both experiments. ANOVA revealed significant effects for each treatment {TPM *vs* SAL: [$F(1,84) = 8.08$, $p < 0.01$]; CLO *vs* SAL: [$F(2,84) = 18.41$, $p < 0.001$]; DIZ *vs* SAL: [$F(1,84) = 1371.46$, $p < 0.0001$]}. A significant difference between prepulse levels was also found [$F(2,168) = 63.28$, $p < 0.001$]. Remarkably, a main interaction effect pretreatment 1 × pretreatment 2 × treatment was also found [$F(2,84) = 12.10$, $p < 0.0001$]; as shown in Figure 7, *post hoc* comparisons assessed that the treatment with clozapine (5 mg/kg, i.p.) significantly attenuated dizocilpine-mediated PPI disruption ($p < 0.01$, Tukey). Surprisingly, this effect was countered by TPM pretreatment ($p < 0.01$ for TPM + CLO + DIZ *vs* SAL + CLO + DIZ).

DISCUSSION

The results of the present study show that TPM affects startle response and sensorimotor gating in rats in a composite, polymorphous fashion. In detail, our findings suggest that this anticonvulsant, albeit able to reduce startle reflex at high dosages, enhances baseline prepulse inhibition within a dose range that does not interfere with startle

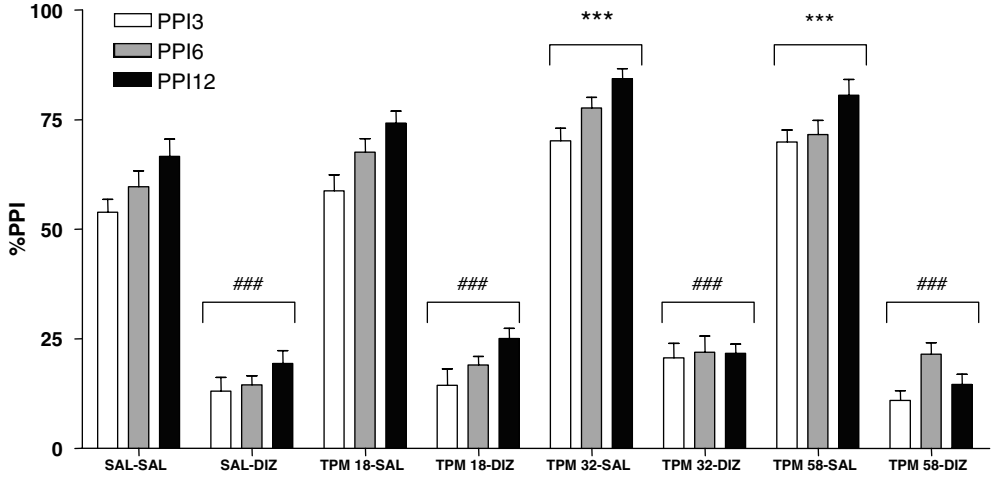

Figure 5 Effect of TPM pretreatment *vs* dizocilpine-induced PPI deficit. All TPM and dizocilpine doses are given in mg/kg. Values represent mean ± SEM for each treatment. Prepulses are indicated by the intensity corresponding to decibels above background noise. SAL, saline; TPM, TPM; DIZ, dizocilpine. $^{***}p < 0.001$, $^{###}p < 0.001$ compared to SAL + SAL group. For further details, see text.

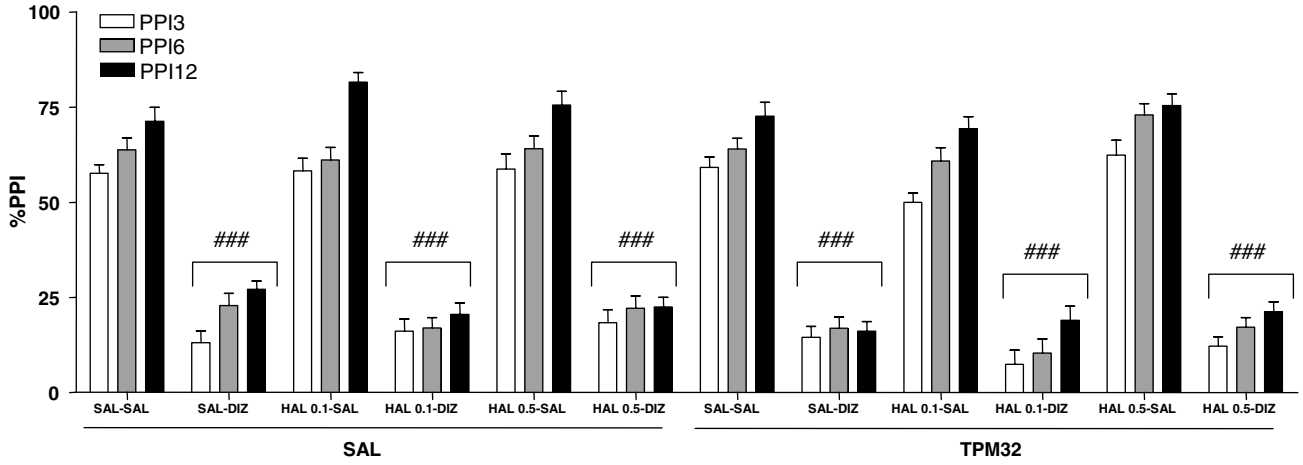

Figure 6 Failure of the combined treatment TPM + haloperidol in antagonizing the dizocilpine-induced deficit in PPI. All doses are given in mg/kg. Values represent mean ± SEM for each treatment. Prepulses are indicated by the intensity corresponding to decibels above background noise. SAL, saline; TPM, TPM; HAL, haloperidol; DIZ; dizocilpine. $^{###}p<0.001$ compared to the respective control group; For further details, see text.

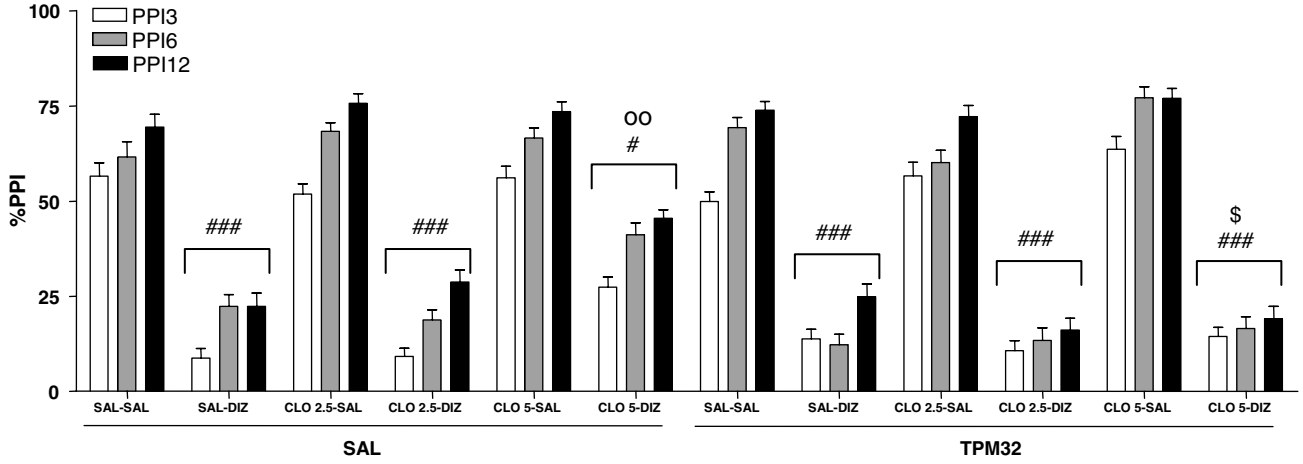

Figure 7 Effect of the combination of TPM and clozapine *vs* PPI deficits induced by dizocilpine. Values represent mean ± SEM for each treatment. All doses are given in mg/kg. Prepulses are indicated by the intensity corresponding to decibels above background noise. SAL, saline; TPM, TPM; CLO, clozapine; DIZ; dizocilpine. $^{#}p<0.05$; $^{###}p<0.001$ compared to the respective control group; $^{oo}p<0.01$ compared to SAL + DIZ subgroup in the SAL pretreatment group; $^{\$}p<0.05$ compared to CLO + DIZ subgroup in the SAL pretreatment group. For further details, see text.

responses. In parallel, TPM has been shown to significantly prevent the disruption of prepulse inhibition induced by the D_1/D_2 dopamine receptor agonist apomorphine, but not by the noncompetitive NMDA receptor antagonist dizocilpine. TPM also potentiates the antipsychotic-like effects of haloperidol and clozapine in reversing apomorphine-dependent PPI deficit. Conversely, the same drug fails to reverse PPI deficits induced by dizocilpine in combination with haloperidol, and even might arguably counter the ability of clozapine to attenuate this phenomenon.

Effects of TPM on Startle Reflex

TPM significantly altered startle amplitude at the dose of 100 mg/kg (i.p.), but not at any of the lower doses administered. As mentioned in the introduction, TPM produces a variety of inhibitory pharmacological and physiological effects relevant to acoustic startle response (ASR), including AMPA receptor antagonism (Gibbs *et al*, 2000), blockade of voltage-gated Na^+ channels (Taverna *et al*, 1999), and particularly GABA activation (White *et al*, 1997). Assuming that the observed reduction in startle reflex may reflect the GABAergic mechanism of TPM, our data appear to align to previous results from our group, indicating that GABAergic activators determine a dose-dependent decrease in startle amplitude (Bortolato *et al*, 2004). Previous evidence suggests that animals treated with a subchronic administration of TPM exhibit dramatic startle response reductions only after exposure to stressors (Khan and Liberzon, 2004). This finding might complement our results in suggesting that TPM might affect reactivity to environmental stimuli only at high doses or under facilitating conditions. Throughout the study, comparisons between average startle amplitudes related to blocks suggest that TPM is unable to significantly affect startle habituation. However, the protocol used in the present study was not optimized for the fine analysis of this paradigm, as shown by the fact that it also failed to detect the well-known ability

of dizocilpine to impair startle habituation (Wang *et al*, 2003; Klamer *et al*, 2004).

Intrinsic Effects of TPM on Prepulse Inhibition

Our experimental results indicate that TPM enhances PPI in a dose-dependent, inverse U-shaped fashion. Ongoing studies and previous experiments by our group suggest that neither GABAergic activators nor AMPA receptor antagonists are conducive to PPI enhancement, plausibly indicating that this effect is likely due to other mechanisms. The neurobiological significance of enhancements in baseline PPI is not fully elucidated, but it does not seem specifically related to antipsychotic activity. In fact, while the ability of antipsychotic drugs to increase baseline PPI has been occasionally shown (Depoortere *et al*, 1997; Sipes and Geyer, 1997; Zhang *et al*, 2000), it has also been proposed to depend on experimental artifacts, since the bulk of evidence has denoted no such effect (Geyer *et al*, 2001). More interestingly, PPI enhancements might reflect an improvement in preattentional and executive functions. In support of this possibility, such a phenomenon has been consistently shown for nicotine (Acri *et al*, 1994; Kumari *et al*, 1996), a well known enhancer of executive behaviors (Granon *et al*, 2003). Further studies are warranted to qualify the significance of TPM-mediated PPI enhancement.

Effects of TPM on Apomorphine-Induced PPI Disruption

The second experiment showed that TPM prevents apomorphine-mediated PPI disruption at doses that also inherently enhance PPI. It could be debated that the observed reversal of apomorphine-mediated PPI disruption might reflect nonspecific enhancements in baseline PPI. The finding, however, that TPM produced no such enhancement in PPI in cotreatment with dizocilpine argues strongly against this possibility. Moreover, statistical comparisons assessed significant differences in %PPI between animals treated with the combination of saline + apomorphine and the controls injected twice with saline, but not between the correspondent groups receiving TPM as pretreatment. While our findings do not allow to determine the mechanism involved in the reversal of apomorphine-induced PPI disruption mediated by TPM, they suggest that the latter might indirectly block the effects mediated by D_2 receptors. In consideration of the postsynaptic mechanism of action of apomorphine on sensorimotor gating (Mansbach *et al*, 1988; Geyer *et al*, 2001), it is also likely that TPM might elicit its action beyond the dopaminergic synapses. Irrespective of the mechanism, our results are in agreement with several other preclinical studies showing that TPM, at comparable doses, elicits antidopaminergic effects on rodents. Previous studies indeed have shown that subchronic TPM attenuates the hyperlocomotion induced by the selective dopamine D_2 receptor agonist quinpirole (Shaldubina *et al*, 2002). Furthermore, TPM has been suggested to modulate the meso-cortico and meso-limbic dopamine function (Moghaddam and Bolinao, 1994) through suppression of the extracellular release of dopamine by simultaneous facilitation of GABA transmission through a non-BDZ site and antagonizing the effects of AMPA and kainate on dopaminergic neurons (Johnson, 2005). There is also evidence demonstrating that TPM can attenuate nicotine-associated rises in nucleus accumbens release of dopamine (Schiffer *et al*, 2001). However, a recent study by Eltayb *et al* (2005) reported that TPM potentiated antipsychotic-like effects of the D_2 receptor antagonist raclopride without affecting accumbal dopamine release.

Effects of TPM on Dizocilpine-Induced PPI Disruption

TPM failed to reverse the PPI disruption produced by the noncompetitive NMDA receptor antagonist dizocilpine. Interestingly, Deutsch *et al* (2002) reported that TPM antagonized dizocilpine-induced mouse popping behavior, an animal model with relevance to NMDA receptor hypofunction in schizophrenia and predictive validity for antipsychotic activity (for a review, see Deutsch *et al*, 1997). The apparent contrast between these findings and our results might be accounted by substantial differences in behavioral traits and pharmacology between mouse popping and dizocilpine-induced prepulse inhibition reduction. Dizocilpine induces popping plausibly through a dopaminergic mechanism, since haloperidol is able to reverse this behavior in a dose-dependent manner (Deutsch and Hitri, 1993). In contrast, the weight of evidence supports the idea that dizocilpine-mediated PPI disruption is mainly independent by dopaminergic mechanisms, although it might be potentiated by acute D_1 receptor activation (Bortolato *et al*, 2005) or blunted by chronic D_2 agonist treatment (Krupin and Hammer, 2005). Indeed, atypical, but not typical antipsychotics, are able to attenuate dizocilpine-induced PPI deficits (Keith *et al*, 1991), suggesting that D_2 receptors are not critically involved in the psychotomimetic mechanisms of NMDA receptor antagonists. A second arguable difference between PPI deficit and mouse popping is that, while the explosive nature of this motor behavior is suggestive of a striatal involvement, dizocilpine fails to disrupt PPI when directly infused in nucleus accumbens (Bakshi and Geyer, 1998).

Effects of TPM on PPI in Combination with Antipsychotics

An interesting corollary of the present study consists in the assessment of the ability of TPM to potentiate the antipsychotic-like activity of both haloperidol and clozapine on apomorphine-mediated PPI disruption. Conversely, TPM did not elicit any adjuvant effect in combination with the same drugs against the deficit in PPI mediated by dizocilpine, and even arguably countered the ability of clozapine to attenuate this latter phenomenon. As mentioned in the introduction, alterations in sensorimotor gating encompass various psychiatric disturbances, characterized by different neurobiological substrates. Schizophrenia itself is a very heterogeneous disorder, the clusters of which probably correspond to profound differences in brain mechanisms. In absence of univocal aetiologic and pathophysiological standards, nosological classifications of psychotic phenomena are exclusively based on symptomatologic criteria. The present study has shown that TPM display opposite actions in cotreatment with the atypical antipsychotic clozapine against two separate pharmacolo-

gical models of filtering deficits. Although the mechanisms accounting for these differences are still elusive, our results might help provide a theoretical framework for the analysis of the differences between PPI disruption endophenotypes, which in turn might mirror diversity in substrates between clusters of psychoses or perceptual disturbances. Irrespective of the mechanisms, however, the present study is in agreement with other reports about the ability of TPM to improve the effect of other antipsychotics in schizophrenic (Drapalski *et al*, 2001; Deutsch *et al*, 2003; Tiihonen *et al*, 2005) as well as in bipolar patients (Chen *et al*, 2005). In parallel, our findings might also help provide a tentative explanation for the numerous discrepancies in literature about the lack of efficacy—or even the hazardous effects—of TPM in combination with other antipsychotic drugs (Dursun and Deakin, 2001; Hofer *et al*, 2003). These conflicting results might indeed depend on differences in the neurobiological substrates underpinning psychotic behaviors and perceptual disfunctions. In light of this possibility, the present study encourages further investigations to explore such differences, and their relevance to the identification of improved therapeutic strategies targeting schizophrenia-spectrum and bipolar disorders.

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