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ORIGINAL INVESTIGATION

Disruption of prepulse inhibition of the startle reflex by the preferential D_3 agonist ropinirole in healthy males

Stella G. Giakoumaki · Panos Roussos · Sophia Frangou · Panos Bitsios

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Abstract
Rationale Emerging evidence from agonist–antagonist studies suggests a role for the dopamine D_3 receptor subtype in the regulation of PPI in animals, but such evidence is lacking for human subjects.
Objectives This study examines the effect of the preferential D_3 agonist ropinirole on PPI in humans.
Methods PPI was tested in 12 healthy men in three sessions associated with ropinirole 0.25 mg, ropinirole 0.5 mg, or placebo according to a balanced, crossover, double-blind design. Two prepulses (75- and 85-dB white noise bursts) and two lead intervals (50 and 80 ms) were employed.
Results Ropinirole 0.5 mg significantly reduced prepulse inhibition (PPI) with both prepulses at the 80-ms lead intervals. There was no effect of treatment on startle amplitude and habituation.
Conclusions These results suggest a role for the dopamine D_3 receptor in the mediation of human PPI, although a contribution from ropinirole's agonistic activity at the D_2 receptor cannot be entirely excluded. Firm conclusions on the role of the D_3 receptor in the modulation of human PPI can only be drawn with the use of genetic approaches or more selective ligands for this receptor.

Keywords Prepulse inhibition · Ropinirole · D_3 receptors · Healthy males

S. G. Giakoumaki · P. Roussos · P. Bitsios (✉)
Department of Psychiatry and Behavioral Sciences,
Faculty of Medicine, University of Crete,
P.O. Box 2208, Heraklion 71003 Crete, Greece
e-mail: pbitsios@med.uoc.gr

S. Frangou
Section of Neurobiology of Psychosis, Institute of Psychiatry,
London, UK

Introduction

Prepulse inhibition (PPI) of the acoustic startle response refers to a reliable reduction in the magnitude of the blink reflex component of the startle response to a strong auditory stimulus (the pulse) if this is preceded by 30–500 ms by a weak stimulus (the prepulse). PPI is considered a measure of "sensorimotor gating", whereby prepulses reduce the effect of subsequent sensory stimuli to protect the brain from sensory overload (Braff and Geyer 1990). PPI is demonstrable across species from mice to humans (Graham 1975), and it is disrupted in neuropsychiatric disorders that are characterized by an inability to gate incoming sensory information such as schizophrenia (Braff et al. 2001). The PPI deficits observed in schizophrenia can be mimicked in animals by the administration of dopamine (DA) agonists. Moreover, typical and atypical antipsychotic drugs reverse the PPI deficits observed in schizophrenic patients (Kumari and Sharma 2002) and hyperdopaminergic animals (Mansbach et al. 1988; Geyer et al. 2001). The D_2 family of receptors are involved in the regulation of PPI in rats (Peng et al. 1990), although there is evidence for a role for the D_1 family as well (Swerdlow et al. 2006). Among the D_2 receptor family (D_2, D_3 and D_4), the DRD_2 subtype appears to be essential for the modulation of PPI (Caine et al. 1995; Ralph et al. 1999), although emerging evidence from agonist–antagonist studies suggests a role for the DRD_3 receptor as well (Bristow et al. 1996; Varty and Higgins 1998; Swerdlow et al. 1998; Reavill et al. 2000; Park et al. 2005). There is growing evidence supporting a role for the DRD_3 receptors in the pathophysiology and treatment of schizophrenia (see Joyce and Gurevich 1999 and Sokoloff et al. 2006 for reviews). The distribution of the D_3 receptor suggests that its functions are related to the mesolimbic rather than the nigrostriatal DA system (Sokoloff et al. 1990). In the human brain, the highest

expression of the D_3 receptor is in the ventral and the association striatum (Murray et al. 1994; Meador-Woodruff et al. 1996; Morissette et al. 1998; Gurevich and Joyce 1999). Gurevich and Joyce (1999) have reported an overlap in the expression of D_3 and D_2 receptors, as D_3 messenger RNA (mRNA) is expressed in at least 30% of the neurons of the ventral striatum and D_2 mRNA in over 75% of the neurons. A detailed understanding of the specific role of the DRD_3 receptor subtype in the modulation of human PPI may help clarify important aspects of the pathophysiology of neuropsychiatric disorders characterised by deficient sensorimotor gating.

In the present study, we examined the effect of ropinirole on PPI in healthy males. Ropinirole is a preferential $D_{3/2}$ agonist (Gerlach et al. 2003) with a 20-fold selectivity for D_3 over D_2 receptors (Reavill et al. 2000), but it also has affinity for the DRD_4 subtype (Newman-Tancredi et al. 2002). The DRD_4 subtype may also play a role in PPI modulation, as selective D_4 antagonists restore amphetamine-induced PPI deficits in mice (Mansbach et al. 1998; Okuyama et al. 1999; Boeckler et al. 2004), although negative results have also been reported (Bristow et al. 1997). While administration of agents that facilitate DA neurotransmission reliably disrupts PPI in animal studies (Mansbach et al. 1988; Swerdlow et al. 1998, 2001, 2002, 2003; Geyer et al. 2001), results in humans seem to depend on study design and baseline PPI at pretest (Bitsios et al. 2005). Thus, subjects in the present study were selected as in Bitsios et al. (2005) for high startle reactivity and PPI at pretest, and a within-subject design was adopted. We used a range of stimulus parameters designed to explore potential stimulus-dependent effects of the drug.

Materials and methods

General procedures

The study was approved by the Ethics Committee of the University of Crete. All participants gave their written informed consent before screening. All participants underwent physical and psychiatric assessment using the Mini-International Neuropsychiatric Interview (Sheehan et al. 1998) and a hearing test. After screening, subjects participated in a preliminary startle-testing session for the assessment of startle reactivity and %PPI at pre-test as in Bitsios et al. (2005). We restricted the sample to men to avoid additional PPI variability related to gender (Swerdlow et al. 1993, 1995, 1997; Weike et al. 2000) and menstrual cycle in women (Swerdlow et al. 1997; Jovanovic et al. 2004; Braff et al. 2005). In line with Bitsios et al. (2005), we included subjects with initial startle reactivity >50 digital units (2.44 μV/digital unit) to eliminate possible confounds from within- and between-session startle habituation (Blumenthal 1996, 1997) in the calculation of %PPI in individuals with low startle amplitudes. Additional inclusion criteria included (a) right-handedness, (b) absence of personal history of head trauma, (c) medical and neurological conditions or use of prescribed and recreational drugs, (d) absence of personal or family (up to second degree relatives) history of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I disorders, (e) hearing threshold of 1 kHz >20 dB and (f) % PPI at pre-test >30 due to the better response of this group of subjects to dopaminergic agents (Bitsios et al. 2005).

Subjects

Thirteen healthy male medical students volunteered for this experiment, but one failed to meet inclusion criteria at screening. Twelve subjects aged 20–31 years (mean±SD, 26.1±3.5) participated in the full study protocol. Eight subjects were non-smokers, and four subjects smoked 10–20 cigarettes/day. All subjects were regular caffeine (two cups of coffee/day on average) and occasional alcohol consumers.

Design and drugs

One to 3 days after screening, all subjects participated in three testing sessions 10 days apart, having been instructed to maintain their normal patterns of caffeine and nicotine consumption to avoid possible effects of caffeine (Swerdlow et al. 2000) and nicotine withdrawal (Kumari and Gray 1999) on PPI. Ropinirole hydrochloride (0.25 and 0.5 mg) and placebo were administered. The choice of the doses of ropinirole was based on this drug's tolerability (British National Formulary 2006). Testing was carried out 1.5 h post-administration at the time of ropinirole's peak effect (Factor 1999). Subjects were allocated to sessions and treatments according to a balanced, crossover, double-blind design.

Startle response measurement

A commercially available electromyographic (EMG) startle system (EMG SR-LAB, San Diego Instruments, San Diego, CA, USA) was used to examine the eyeblink component of the acoustic startle response. This was used to deliver acoustic startle stimuli and record the EMG activity for 150 ms (sample interval=1 ms) starting from the onset of the startle stimulus, and the raw data were stored for later application of rejection criteria and averaging. Acoustic stimuli were administered binaurally through headphones (model TDH-39-P, Maico, Minneapolis, MN, USA). EMG recordings were taken while subjects were seated comfortably in an armchair and instructed to relax but stay awake.

The eyeblink component of the startle reflex was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye by positioning two miniature silver/silver chloride electrodes filled with Signa Gel electrolyte paste (Parker Laboratories, New Jersey, USA) with a ground electrode behind the right ear on the mastoid ($R<10$ kΩ). EMG activity was band-pass filtered (100–1,000 Hz) and a 50-Hz filter was used to eliminate the 50-Hz interference. Pulses consisted of 40-ms, 115-dB white noise bursts and prepulses consisted of 20-ms of either 75- or 85-dB white noise bursts over a 70-dB background noise. Recording began with 3 min of acclimation period when only the background noise was present. The recording period consisted of 46 trials. There were two blocks of five pulse-alone trials, one at the beginning and one at the end of the recording session, with one block of 36 trials in between. The startle responses to the initial and final pulse-alone blocks were used to estimate startle habituation as per Vollenweider et al. (1999) and were not included in the calculation of PPI. The 36-trial block consisted of 12 pulse-alone and 24 prepulse–pulse trials. Two lead intervals (onset to onset) were used: 50 and 80 ms. For each lead interval, there were six trials with the 75-dB prepulse and six with the 85-dB prepulse. All trials were presented in a pseudorandom order, with the constraint that no two identical trials occurred in succession. The inter-trial interval varied between 9 and 23 s (average 15 s). The entire session lasted approximately 15 min.

Before scoring and data analysis, all recordings were screened for spontaneous eyeblink activity. Trials were excluded if excessive EMG activity (>20 digital units= 48.8 μV) as observed during the first 20 ms of the recording or when onset latencies (defined by a shift of 20 digital units from the baseline value, occurring within 20–85 ms after the onset of the pulse stimulus) and peak latencies (the point of maximal amplitude) differed by more than 95 ms (Braff et al. 1992, 1999). About 1% of trials across all drug and placebo conditions were excluded using these criteria. No subjects had more than two (out of six) trials per trial type discarded at any one session. The maximum absolute amplitude of the raw EMG data occurring in the 20–150 time window of the non-rejected trials was scored offline and stored for averaging and data analysis.

Statistical analysis

(a) Data from the first five pulse-alone trials from the beginning and the end of the startle testing session were averaged separately for each block, and the respective means were subjected to a 3×2 (treatment × block) repeated-measures analysis of variance (ANOVA) to examine treatment effects on startle and startle habituation. (b) The maximal amplitudes of the raw EMG responses from each trial were averaged across all trials of the same type. Percentage PPI (%PPI) was calculated using the formula $[(\text{amplitude}_{\text{pulse-alone}} - \text{amplitude}_{\text{prepulse-pulse}})/\text{amplitude}_{\text{pulse-alone}}] \times 100$. %PPI data were analysed by a 3×2×2 (treatment × prepulse intensity × lead interval) repeated-measures ANOVA. Significant effects involving treatment were further examined by comparing the active treatment to placebo using Dunnett's tests.

Results

Startle amplitude and habituation

Startle amplitudes (mean±SEM) in the first and last blocks used to test the effects of treatment on startle amplitude and habituation are seen in Table 1. There was no significant main effect of treatment or treatment by block interaction [$F(2, 22)=2.24$; $p>0.1$ and $F(2, 22)=1.43$; $p>0.1$, respectively], but a significant block main effect was found [$F(1, 11)=45.23$; $p<0.001$; partial $\eta^2=0.8$; observed power=1.0], indicating significant startle habituation.

Prepulse inhibition

Figure 1 shows the %PPI after administration of placebo or ropinirole 0.25 and 0.5 mg in trials with 75- or 85-dB prepulses at 50- and 80-ms lead interval types. A 3×2×2 (treatment × prepulse × interval) repeated measures ANOVA revealed a significant treatment × lead interval interaction [$F(2, 22)=4.87$; $p<0.02$; partial $\eta^2=0.31$; observed power=0.75], and post hoc analyses showed significant reductions of PPI with ropinirole 0.5 mg at trials with both 75- and 85-dB prepulses and 80-ms lead intervals. There were also significant prepulse intensity and lead interval main effects [$F(1, 11)=36.93$; $p<0.001$; partial $\eta^2=0.77$; observed power=1.0 and $F(1,11)=25.70$; $p<0.001$; partial $\eta^2=0.7$; observed power=0.99, respectively], but the treatment main effect and all other interactions were not significant [all F values <1; prepulse intensity × lead interval [$F(1, 11)=3.09$; $p>0.1$)].

Table 1 Startle amplitudes (mean±SEM) in the first and last blocks used to test the effects of treatment on startle amplitude and habituation

	Placebo	Ropinirole 0.25 mg	Ropinirole 0.5 mg
First block	142.23±22.9	165.87±26.7	163.11±28.9
Last block	98.52±20.9	102.52±23.9	95.20±19.8

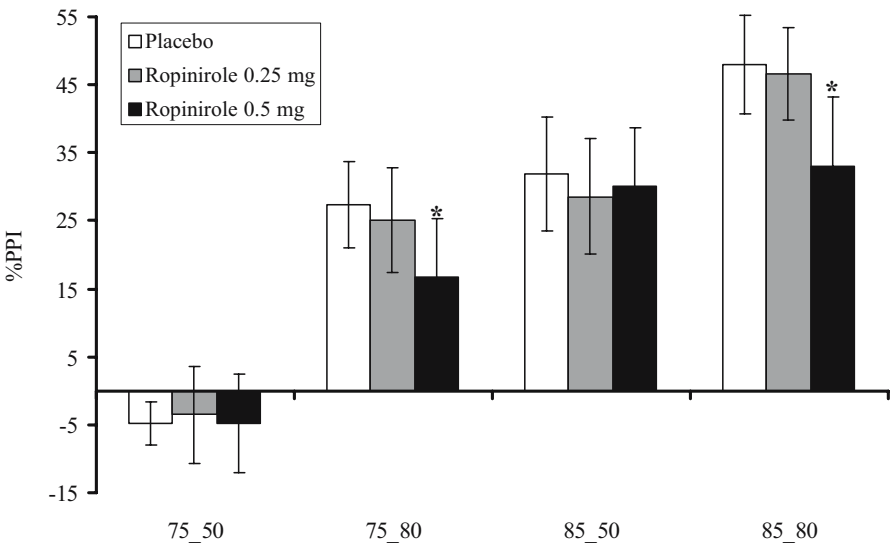

Fig. 1 Percentage prepulse inhibition (%PPI) with two prepulses at two lead intervals, under placebo and ropinirole 0.25 and 0.50 mg. *Columns* represent group means and *bars* represent SEMs

*: Significantly different from placebo

Discussion

To our knowledge, this is the first study to show that ropinirole at 0.5 mg disrupts PPI in healthy individuals. At this dose, ropinirole did not affect baseline startle or startle habituation indicating that (a) PPI disruption by ropinirole cannot be attributable to changes in startle characteristics and (b) startle amplitude and habituation are not affected by changes in dopaminergic neurotransmission. In clinical pharmacology, ropinirole is given at a starting dose of 0.25 mg to minimise the potential of side effects from a sudden increase in central dopaminergic neurotransmission (BNF 2006). This dose had no effect on PPI in our study confirming that its effect on dopaminergic systems is minimal. Our results agree with animal studies, which have shown that ropinirole disrupts PPI in the rat (Swerdlow et al. 1998), without affecting startle amplitude or habituation.

Ropinirole is a mixed $D_{3/2}$ agonist with a 20-fold selectivity for D_3 over D_2 receptors (Reavill et al. 2000). It is therefore likely that the ropinirole-induced PPI disruption was mediated through agonism at the D_3 receptor, although a contribution from agonistic activity at the D_2 receptor cannot be entirely excluded. The D_3 receptors are expressed preferentially in subcortical basal ganglia and limbic structures (Sokoloff et al. 1990; Jackson and Westlind-Danielsson 1994; Schwartz et al. 2000), which are functionally associated with the modulation of prefrontal cortex (PFC) functions (Morissette et al. 1998), due to their dopaminergic projections to the PFC (Sesack and Carr 2002, for review). One possibility is that ropinirole reduced PPI by activation of subcortical presynaptic D_3 autoreceptors, which inhibit ventral tegmental dopaminergic neurons, thus reducing the DA levels in the PFC (Lejeune and Millan 1995; Gobert et al. 1996).

The role of the PFC in PPI in humans is supported by functional imaging studies of PPI (Hazlett et al. 2001; Kumari et al. 2003), and there is evidence that PPI is modulated by cognitive processes controlled in a "top–down" fashion by the PFC (Hazlett et al. 2001; Giakoumaki et al. 2006; Bitsios et al. 2006). We have also shown recently that PPI is influenced by the Val/Met COMT polymorphism in a manner suggestive of a linear association between PFC DA levels and PPI in healthy subjects (Roussos et al. 2006). The ropinirole-induced PPI disruption at the 80- but not 50-ms lead interval is perhaps best explained by a DRD_3-mediated reduction of PFC DA levels; one corollary of this proposal is that 50 ms would be too short an interval for cognitive "top–down" influences from the PFC to fully exert their modulatory effect on the subcortical startle circuit. Indeed, independent evidence from attention-to-prepulse paradigms has shown that intervals up to 60 ms, but not lower, may be prone to selective attention effects (Thorne et al. 2005), and we have shown that performance in PFC-dependent tasks correlates with PPI at 80 ms lead interval (Giakoumaki et al. 2006; Bitsios et al. 2006). Moreover, functional magnetic resonance imaging (fMRI) studies have shown that PPI at longer (120 ms), but not shorter (30 ms), lead intervals is associated with cortical activation (Kumari et al. 2006).

Alternatively, the effect of ropinirole on PPI could also be due to D_3 agonism at extrastriatal sites such as the CA1 area of the dorsal hippocampus, as local hippocampal application of the D_3 agonist quinpirole reduces PPI in the rat (Ellenbroek et al. 2002).

In the present study, subjects were selected on the basis of relatively high startle reactivity as in the study of Bitsios et al. (2005) and high baseline PPI, as these subjects are more susceptible to potential PPI-disruptive effects of dopaminergic agonists (Bitsios et al. 2005). The present

results may not generalize to subjects with low startle reactivity and/or low basal PPI.

There is evidence against a D_3 involvement in the mediation of the observed ropinirole-induced PPI reduction. Zhang et al. 2006 showed that preferential D_3 antagonists had either no effect or were required at higher doses to reverse the strain-specific PPI deficit in the DBA/2J mice. However, there are species differences in D_3 receptor distribution (Diaz et al. 2000; Gurevich and Joyce 1999), and we have no information about D_3 distribution, density and intrinsic activity in the DBA/2J mice. Firm conclusions on the role of the D_3 receptor in the modulation of human PPI can only be drawn with the development of more selective ligands for this receptor or perhaps with the use of genetic approaches. One such possibility may be the testing of existing preferential D_3 agonists in subjects characterized for the DRD_3 Ser9Gly polymorphism, which determines the gain of function of the D_3 receptor as assessed by increased dopamine affinity and signaling responses in Gly-9 homozygous individuals (Jeanneteau et al. 2006). These issues may be important for determining the neural basis of deficient sensorimotor gating in schizophrenia and may facilitate the development of novel pharmacotherapies and/or treatment strategies of schizophrenia.

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