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Quinelorane, a dopamine D3/D2 receptor agonist, reduces prepulse inhibition of startle and ventral pallidal GABA efflux: Time course studies

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Abstract

Startle is inhibited when the startling stimulus is preceded 30–300 ms by a weak prepulse. Prepulse inhibition (PPI), an operational measure of sensorimotor gating, is deficient in schizophrenia patients, and reduced in rats and humans by dopamine agonists. The neural basis for the PPI-disruptive effects of dopamine agonists in rats is studied to understand neural circuitry regulating PPI and its deficits in schizophrenia. Existing data suggest that ventral pallidal (VP) GABAergic transmission regulates PPI and its disruption by dopamine agonists. We measured changes in VP GABA efflux and PPI in rats in response to the D2/D3 agonist, quinelorane. Wistar rats were administered quinelorane (vehicle, 0.003 or 0.01 mg/kg). In some rats, VP dialysate was analyzed for GABA content. In others, PPI was assessed using 120 dB(A) startle pulses and prepulses 10 dB over a 70 dB(A) background. Quinelorane reduced GABA efflux, with significant effects for 0.01 but not 0.003 mg/kg, persisting for at least 100 min. Quinelorane reduced PPI for 50 min, an effect significant for both the 0.003 ($p < 0.05$) and 0.01 mg/kg doses ($p < 0.015$). Differences in time course and dose sensitivity of quinelorane effects on VP GABA efflux and PPI are discussed.

Keywords

gamma amino butyric acid (GABA); microdialysis; capillary electrophoresis-coupled laser-induced fluorescence (CE-LIF); dopamine; quinelorane; prepulse inhibition; schizophrenia; startle

1. Introduction

Prepulse inhibition (PPI) of the acoustic startle response is a cross-species measure of sensorimotor gating, in which the startle response is reduced when the startling stimulus is preceded by a weaker prepulse (Davis et al., 1982; Hoffman and Ison, 1980). PPI is reduced in patients with schizophrenia and other specific neuropsychiatric disorders, and in rats after manipulations of limbic cortex, striatum, pallidum or pontine tegmentum (“CSPP” circuitry)

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(cf. Braff et al., 2001; Swerdlow et al., 2001). Limbic CSPP circuitry has been studied in rats to reveal the neurochemical and neuroanatomical substrates regulating PPI at a high level of resolution. In translational cross-species research, this detailed circuit information is used as a “blueprint” to identify substrates that may lead to PPI deficits in psychiatrically disordered humans (Swerdlow et al., 2001).

Substantial progress has been made towards identifying the brain circuitry that regulates PPI. For example, PPI is regulated by dopaminergic receptors, with perhaps the strongest evidence supporting a primary role for the “D₂-like” family of receptors within the nucleus accumbens (NAC) (Caine et al., 1995; Wan et al., 1994). Neural activity in the hippocampus, amygdala and prefrontal cortex also regulates PPI, conceivably via their direct or indirect subcortical projections to the NAC (cf. Swerdlow et al., 2001). One major mesolimbic “output” pathway arising within NAC is a dense GABAergic projection into the subpallidal regions that include the ventral pallidum (VP) (Jones and Mogenson, 1980a, b). This striato-pallidal projection thus forms the next segment of a pervasive neural circuit regulating central inhibitory mechanisms in mammals (Mogenson, 1987).

Decreased PPI after NAC DA activation might reflect reduced activity in GABAergic projecting from the NAC to VP. Consistent with this, the PPI-disruptive effects of NAC DA infusion or cell lesions of the NAC in rats are reversed by infusion of the GABA agonist muscimol into the VP (Kodsi and Swerdlow, 1994; Swerdlow et al., 1990) or ibotenic acid lesions of the VP (Kretschmer and Koch, 1998), and are reproduced by subpallidal infusion of the GABA antagonist picrotoxin (Kodsi and Swerdlow, 1995; Swerdlow et al., 1990). While these studies provide a strong inference that accumbens-mediated decreases in PPI result from reduced VP GABA activity, there is no direct evidence that decreased VP GABA efflux accompanies the PPI-disruptive effects of DA agonists.

The aim of the present study is to elucidate further the involvement of VP GABAergic activity in the PPI-disruptive effects of DA agonists. Experiments were conducted to investigate the dose and time-course effects of the dopamine D₃/D₂ agonist, quinolorane on PPI and VP GABA release. “Quinelorane exhibits high D₃ affinity, and selectivity for D₃ over D₂ receptors in vitro (Levant, 1997; Shafer and Levant, 1998). In vivo, quinolorane exhibits both behavioral and electrophysiological effects consistent with predominant D₃ activation (Ireland et al., 2005).”

2. Materials and Methods

2.1. Experimental animals

A total of 32 male Wistar rats (300 g, Charles River, Wilmington, MA) were used. All animals were housed in a temperature-controlled vivarium (22°C) with reverse 12 h light/dark cycle, and given *ad libitum* access to food and water. All behavioral testing took place in the dark phase. Rats were handled within 48 h of arrival and allowed to acclimate to the laboratory for 7 days prior to behavioral testing. The studies were conducted in accordance with the *Guide for Care and Use of Laboratory Animals* provided by the National Institutes of Health. Quinelorane and all other reagents and neurotransmitter standards were obtained from Sigma (St Louis, MO, USA).

2.2. Apparatus and PPI testing procedures

Startle chambers (SR-LAB Startle Reflex System; San Diego Instruments) were located in a sound-attenuated room with 60 dB ambient noise. Rats were exposed to a brief ‘matching’ startle session used to assign rats to balanced drug groups according to their average level of PPI. Testing continued 4 days later. After either quinolorane (0.003 and 0.01 mg/kg, s.c.) or vehicle (saline) treatment, all animals were immediately placed in the startle chambers with

a 70 dB(A) background noise that continued throughout the test. A higher dose of quinelorane (0.1 mg/kg) has previously been reported to significantly reduce PPI in rats (Varty and Higgins, 1998), and this was confirmed by pilot studies in our laboratory. Test sessions were approximately 100 min long and consisted of ten 10 min blocks. The initial 5 min of each block included three trial types: 7 PULSE trials (120 dB(A) 40 ms noise burst), 6 prepulse-PULSE trials (20 ms noise burst 10 dB above background followed 100 ms later by PULSE) and 3 prepulse alone trials. NOSTIM trials (behavior measurement without stimulus presentation) were interspersed between trials, but were not included in the calculations of inter-trial intervals (ave. 20 s).

2.3. Microdialysis surgery and sample collection

Rats were anesthetized with Isoflurane/oxygen vapor mixture (1–2%) and stainless steel guide cannulae (21 gauge) were stereotactically lowered to terminate 2 mm above the VP (from Bregma: AP – 0.6 mm; ML $\pm$ 2.2 mm; DV – 6.7 mm (from dura) (Paxinos 1998)) and secured to the skull using cement. Rats recovered from surgery for at least 7 days before experimental testing. After completion of the experiment rats were sacrificed by sodium pentobarbital overdose and Nissl-stained sections were analyzed to verify probe and cannulae placement (Figure 1A).

For microdialysate collection, each rat was lightly anesthetized (1–2% isoflurane) and a microdialysis probe was inserted and secured to the guide cannula (probes described in (Caille and Parsons, 2003)). After probe implantation, rats were placed individually a standard rat cage with bedding, food and a water bottle. Dialysis probes were perfused with artificial cerebrospinal fluid (aCSF) delivered via a liquid swivel at 0.1 μ l/min (pH 7.2–7.4; 149 mM NaCl, 2.8 mM KCl, 1.2 mM CaCl₂, 1.2 mM MgCl₂, 0.25 mM ascorbic acid). Approximately 3 h later the perfusate flowrate was increased to 0.6 μ l/min and dialysate samples were collected in polypropylene tubes at 10-minute intervals over a 60 min baseline period. Rats then received either 0.003 mg/kg (n=5, sc.) or 0.01 mg/kg (n=4, sc.) Quinelorane, and dialysate sampling continued at 10 min intervals for an additional 2 hours. After collection, the samples were frozen on dry ice and stored at –70°C.

2.4. Microdialysis sample analysis

Microdialysate GABA content was determined using capillary electrophoresis (CE) with laser-induced fluorescence (LIF) detection as previously described (Caille and Parsons, 2004, 2006; O'Dell et al., 2006; O'Dell and Parsons, 2004; Roberto et al., 2004a; Roberto et al., 2004b). GABA was derivatized by mixing 4 μ l of microdialysate with 9 μ l of 40 mM borate buffer (pH 10.5) containing 3.8 mM KCN and 1 μ l of 5 mM naphthalene-2,3-dicarboxaldehyde (NDA) in methanol, and detected using a laser-induced fluorescence detector (Zetlif, Picometrics) that employs a 442 nm HeCd laser (30 mW, Melles Griot). External calibration standards were run in duplicate throughout the sample run. The limits of quantification are approximately 1 nM for each of the analytes, which is well below the concentration of GABA typically found in these microdialysis samples (Caille and Parsons, 2004, 2006; O'Dell et al., 2006; O'Dell and Parsons, 2004; Roberto et al., 2004a; Roberto et al., 2004b).

2.5. Data collection and analysis

Between-group differences in baseline microdialysate GABA concentrations were first compared by ANOVA. Following confirmation of no group differences in baseline GABA concentration, the data for each animal were converted to the percent change from the average baseline concentration obtained for 60 min prior to the pretreatment injection. The temporal effect of drug pretreatment on quinelorane-induced changes in dialysate GABA

levels was then evaluated using ANOVA with repeated measures over time, with pretreatment dose as the between-subjects factor.

PPI was calculated as a percent reduction in startle magnitude on prepulse+PULSE trials compared to PULSE trials, i.e. $100 - [(startle \text{ amplitude on prepulse trials} / startle \text{ amplitude on P-ALONE trials}) \times 100]$. Any drug effects on %PPI prompted separate analyses to assess the relationship of these effects to drug-induced changes in startle magnitude on PULSE. All startle data were analyzed using an ANOVA with time and drug treatment as between-subject factors repeated measures. Inspection of the data revealed that quinelorane-induced effects on PPI lasted approximately 50 min, and this epoch served as the period for detailed statistical analyses. Post hoc comparisons of significant interaction effects and relevant main factor effects were conducted using Fisher's protected least significant difference (PLSD) and one-factor ANOVA tests.

3. Results

Baseline GABA concentrations in VP dialysates were stable over 60 minutes, and did not differ between 0.003 and 0.01 mg/kg quinelorane treatment groups ($F < 1$) (39.22 ± 4.27 nM vs. 31.47 ± 2.42 nM, respectively). ANOVA revealed no significant effect of group assignment ($F < 1$), time block ($F = 1.44$, $df 1,5$, NS) or group $\times$ time interaction ($F < 1$). Dialysate data were then expressed as a percent of baseline activity, based on the mean levels across the 60 min pre-drug sampling period (Figure 1B). The higher dose of quinelorane led to a rapid and sustained reduction in GABA efflux, with efflux levels after injection of 0.01 mg/kg declining more than 30% by 20 min post-injection, and by more than 50% by 80 min post-injection. In contrast, maximal suppression of GABA efflux after 0.003 mg/kg quinelorane was 13.4%, evident 70 min post-injection. A within-subject ANOVA compared GABA efflux during the 60 min pre- vs. post-quinelorane injection. This revealed significant effect of injection epoch (pre- vs. post-injection) ($F = 16.41$, $df 1,7$, $p < 0.005$), a significant effect of quinelorane dose ($F = 13.10$, $df 1,7$, $p < 0.009$), and a significant interaction of dose $\times$ epoch ($F = 13.15$, $df 1,7$, $p < 0.009$). Post-hoc comparisons revealed significantly reduced GABA efflux in high- vs. low-dose groups post-injection ($F = 13.13$, $df 1,7$, $p < 0.009$).

Inspection of the behavioral time course revealed that quinelorane reduced PPI (Figure 2A) and startle magnitude (Figure 2B) over the first 50 min of testing. ANOVA of PPI over this time period (Figure 2A) revealed a significant effect of dose ($F = 3.96$, $df 2,21$, $p < 0.04$). Post-hoc comparisons confirmed significant PPI-reducing effects of both 0.003 mg/kg ($p < 0.05$) and 0.01 mg/kg doses ($p < 0.01$) over this period. While there was no significant effect of time ($F < 1$) or dose $\times$ time interaction ($F < 1$), exploratory comparisons revealed reductions of large effect size for the 0.01 mg/kg dose extending from the initial 10 min block ($d = 0.93$) to the final 10 min block ($d = 0.95$); large effects of the 0.003 mg/kg dose were evident only at the 30 min time point ($d = 1.06$).

Quinelorane reduced startle magnitude, with significant effects first detected after 30 minutes of testing (Figure 2B). ANOVA with dose of quinelorane as a between-subject factor and time as a within-factor revealed no significant effect of dose ($F = 1.68$, $df 2,21$, NS), a significant effect of time ($F = 5.68$, $df 4,84$, $p < 0.0001$) and a significant dose $\times$ time interaction ($F = 2.14$, $df 8,84$, $p = 0.04$). Post-hoc comparisons revealed a non-significant trend towards increased startle magnitude over the first 10 min of the test session in rats treated with 0.003 mg/kg quinelorane, followed by a significant quinelorane-induced reduction in startle magnitude over test min 30 – 50 ($F = 5.35$, $df 2,21$, $p < 0.015$; post-hoc comparisons: 0.003 mg/kg: $p < 0.03$; 0.01 mg/kg: $p < 0.005$).

To parse the effects of quinlorane on startle magnitude vs. PPI, dose subgroups were matched ($n=6/\text{dose}$) with nearly identical startle magnitudes during this initial 50 min period ($F<0.25$) (Figure 3 (inset)). ANOVA of PPI in these rats confirmed a significant effect of quinlorane dose ($p<0.003$) (Figure 3). Post-hoc comparisons confirmed significant PPI-reducing effects of both 0.003 mg/kg ($p<0.008$) and 0.01 mg/kg doses ($p<0.002$) over this period.

Analysis of movement-induced signals after prepulses presented alone during this initial 50 min period revealed no significant effects of quinlorane dose ($F < 1$), time ($F = 1.21$, df 4,84, NS) or dose $\times$ time interaction ($F = 1.44$, df 8, 84, NS). Similarly, NOSTIM levels were unaffected by quinlorane dose or time. Overall, 10 dB-over-background prepulses were accompanied by a mean movement-induced signal of 0.9 units; this compares to a mean of 731.2 units in response to P-ALONE trials, and a mean of 0.21 units during NOSTIM trials. When NOSTIM displacement levels are subtracted from prepulse displacement levels, it is evident that prepulses alone elicited a “motor” signal less than 0.1% of that elicited during startle responses.

4. Discussion

Systemic quinlorane administration reduces VP GABA efflux and PPI, and causes significant changes in startle magnitude. A comparison of these three effects, over variables of dose and time, revealed several clear patterns: 1) quinlorane-induced changes in VP GABA efflux were evident within the initial 10 min post-drug epoch, but 2) only at the higher (0.01 mg/kg) dose, and 3) lasted at least 90 min. In contrast, quinlorane-induced changes in PPI were: 1) fully expressed within 10 min, 2) evident at both doses, but 3) lasted only 50 min. These effects of quinlorane on VP GABA efflux and PPI are thus dissociable by dose and time. PPI and VP GABA efflux are both reduced by the high dose of quinlorane, over a time period in which startle magnitude is both increased (10 min) and decreased (min 30–40) by this dose of quinlorane. Thus, quinlorane effects on startle magnitude can be temporally dissociated from those on both PPI and GABA efflux.

The present findings are consistent with the model that VP GABA neurotransmission contributes to the regulation of prepulse inhibition. In previous studies, VP infusion of the GABA antagonist picrotoxin was shown to disrupt PPI (Kodsi and Swerdlow, 1995; Swerdlow et al., 1990). Here, quinlorane caused a decrease in GABA efflux in the VP in one group of rats, at a time that coincided with a reduction in prepulse inhibition in a parallel group of rats. Other support for a PPI-regulatory role of VP GABA transmission comes from evidence that the PPI-disruptive effects of NAC DA infusion are reversed by infusion of the GABA agonist muscimol into the VP (Swerdlow et al., 1990) or ibotenic acid lesions of the VP (Kretschmer and Koch, 1998). Therefore, decreased PPI after activation of NAC DA receptors might reflect reduced activity in NAC GABAergic projections to the VP.

However, if reduced VP GABA efflux is responsible for the PPI-disruptive effects of quinlorane, one must account for the fact that the behavioral change (reduced PPI) was both more sensitive and more fleeting, compared to the neurochemical change (reduced VP GABA efflux).

Certainly, it is possible that the reduction in PPI but not VP GABA efflux after 0.003 mg/kg quinlorane reflects the sensitivity of this behavioral measure to small changes in VP GABA activity. Alternatively, this apparent difference might reflect methodological differences in the behavioral and neurochemical preparations. For example, dialysate sampling occurred immediately after the sc quinlorane injection, while PPI testing was delayed for 5 minutes to allow the rat to habituate to the background white noise. If an “injection artifact” caused

the small “spike” in VP GABA efflux after the 0.003 mg/kg dose, the behavioral consequences might not be detected in PPI testing. We would expect to see a similar “spike” after injection of vehicle (which was not done in the present design), but after injection of 0.01 mg/kg quinelorane, such an effect might be masked by the more potent drug-induced suppression of GABA efflux.

The loss of quinelorane effects on PPI after 50 min (despite the apparent persistence of reduced VP GABA levels) might also reflect the time-dependent reduction in PPI in vehicle-rats, resulting in a “floor effect”. As seen in Figure 2, mean PPI in vehicle-treated rats for minutes 51 – 100 (mean % (SEM) = 34.76 (4.90)) was substantially reduced compared to minutes 0 – 50 (mean % (SEM) = 50.22 (4.17)). Reduced PPI over time could result from stressful effects of sustained startle testing. The present paradigm utilized a test session that was substantially more prolonged than the typical 20–30 minute test. In one published report, PPI measured in a 240 minute session (Zhang et al. 2000) declined over the initial 60 minutes of testing, but later recovered; these measures were conducted in an open arena, which would likely be less stressful than the enclosed Plexiglas tube used for our studies.

Dialysate values in this study assessed GABA levels in the VP, while changes in PPI reflected activity “downstream” from the VP - from the VP GABA receptor, to post-receptor signaling, to events distal to the VP projection targets in the pons and thalamus. Clearly, the “waning” of quinelorane effects on PPI despite persistently reduced VP GABA levels could reflect “accommodation” at any one of these downstream steps, including but not limited to increases in VP GABA receptor sensitivity. A previous report by Zhang et al. (2000) described a close temporal association between reductions in PPI and increases in NAC DA efflux *in the same rats* after systemic administration of d-amphetamine. Even in this report, which provided a striking and elegant demonstration of the convergence of behavior and neurochemistry, inspection of the data (Figure 2, p. 184) suggests that PPI levels returned to pre-drug levels at a time when NAC DA overflow remained at 200% of baseline values. Thus, a perfect temporal concordance of behavior and neurochemistry might not be reasonable to expect, particularly in the present paradigm, in which PPI and dialysis were conducted in different rats.

While there are viable (and testable) explanations for the minor divergence of dose and temporal properties, it is also possible that quinelorane effects on PPI and GABA efflux may be coincidental but not causally linked, and may thus follow different dose and temporal patterns reflecting their distinct underlying neural substrates. This possibility will be tested by assessing the PPI-disruptive effects of quinelorane during intra-VP infusion of either GABA or a GABA agonist. Similar strategies have confirmed that reduced PPI after NAC DA stimulation is prevented by VP GABA stimulation (Swerdlow et al. 1990).

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Figure 1.

A. Schematic representation of the standard location of the 1.5-mm dialysis probe membranes within the ventral pallidum. Distances shown are in mm from Bregma (from Paxinos 1998). B. Effects of quinlorane treatment on VP GABA efflux in male wistar rats. Data are expressed as percentage change from baseline levels (mean $\pm$ SEM).

Figure 2.

Effects of quinolorane treatment on PPI and startle magnitude over min 0 – 50. A. ANOVA of PPI over this time period revealed a significant effect of dose. Post-hoc comparisons confirmed significant PPI-reducing effects of both 0.003 mg/kg and 0.01 mg/kg doses over this period. Comparisons revealed reductions of large effect size for the 0.01 mg/kg dose extending from the initial 10 min block to the final 10 min block; large effects of the 0.003 mg/kg dose were evident only at the 30 min time point. B. Quinelorane had a biphasic effect on startle magnitude over this period. ANOVA revealed no significant effect of dose, a significant effect of time and a significant dose $\times$ time interaction. Post-hoc comparisons revealed a non-significant trend towards increased startle magnitude over the first 10 min of

the test session in rats treated with 0.003 mg/kg quinelorane, followed by a significant quinelorane-induced reduction in startle magnitude over test min 30 – 50.

Figure 3.

Effects of quinelorane treatment on prepulse inhibition of acoustic startle after dose subgroups were matched for comparable startle magnitude (inset) during this initial 50 min period. ANOVA of PPI in these rats confirmed a significant effect of quinelorane dose. Post-hoc comparisons confirmed significant PPI-reducing effects of both 0.003 mg/kg and 0.01 mg/kg doses over this period.