Pharmacology, Biochemistry and Behavior 90 (2008) 686–690

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

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

Ying Qu [a], Neal R. Swerdlow [a,*], Martin Weber [a], David Stouffer [b], Loren H. Parsons [b]

[a] Department of Psychiatry, UCSD School of Medicine, 9500 Gilman Dr., La Jolla, CA 92093-0804, United States
[b] Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, CA 92037, United States

ARTICLE INFO

Article history:
Received 6 March 2008
Received in revised form 12 May 2008
Accepted 22 May 2008
Available online 24 June 2008

Keywords:
Gamma amino butyric acid (GABA)
Microdialysis
Capillary electrophoresis-coupled laser-induced fluorescence (CE-LIF)
Dopamine
Quinelorane
Prepulse inhibition
Schizophrenia
Startle

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.

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) (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; Koch and Schnitzler, 1997).

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 "D_2-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 (Bourdelais and Kalivas, 1992). 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, quinelorane 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*, quinelorane exhibits both behavioral and electrophysiological effects consistent with predominant D3 activation (Ireland et al., 2005)."

* Corresponding author. UCSD School of Medicine, 0804, 9500 Gilman Dr., La Jolla, CA 92093-0804, United States. Fax: +1 619 543 249.
E-mail address: nswerdlow@ucsd.edu (N.R. Swerdlow).

0091-3057/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.pbb.2008.05.012

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 quinelorane (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 stereotaxically lowered to terminate 2 mm above the VP (from Bregma: AP −0.6 mm; ML ±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 (Fig. 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 in 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 µl/min (pH 7.2–7.4; 149 mM NaCl, 2.8 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgCl_2$, 0.25 mM ascorbic acid). Approximately 3 h later the perfusate flowrate was increased to 0.6 µl/min and dialysate samples were collected in polypropylene tubes at 10-min intervals over a 60 min baseline period. Rats then received either 0.003 mg/kg (n=5, s.c.) or 0.01 mg/kg (n=4, s.c.) Quinelorane, and dialysate sampling continued at 10 min intervals for an additional 2 h. 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,b). GABA was derivatized by mixing 4 µl of microdialysate with 9 µl of 40 mM borate buffer (pH 10.5) containing 3.8 mM KCN and 1 µl of 5 mM naphthalene-2,3-dicarboxaldehyde (NDA) in methanol, and detected using a laser-induced fluorescence detector (Zetalif, 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,b).

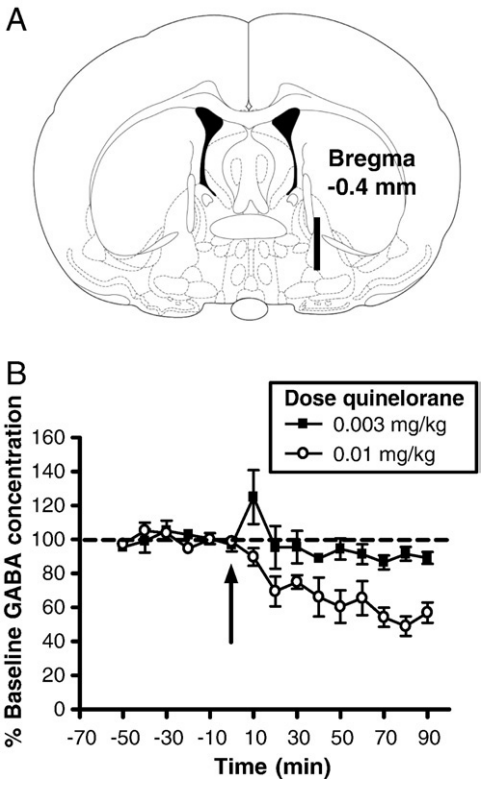

Fig. 1. A. Schematic representation of the standard location of the 1.5-mm dialysis probe membranes within the ventral pallidum. Distances shown are in mm from Bregma (from Paxinos 1998). B. Effects of quinelorane treatment on VP GABA efflux in male Wistar rats. Data are expressed as percentage change from baseline levels (mean ± SEM).

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 amplitude on prepulse trials/startle amplitude on P-ALONE trials)×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

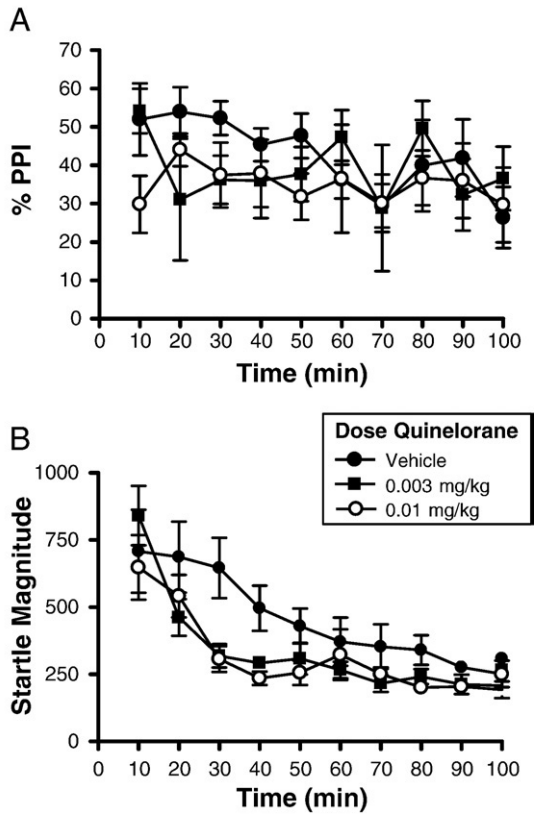

Fig. 2. Effects of quinelorane treatment on PPI and startle magnitude over min 0–100. A. ANOVA of PPI over min 0–50 revealed a significant effect of dose. Post-hoc comparisons confirmed significant PPI-reducing effects of both 0.003-mg/kg and 0.01-mg/kg doses over this period. Comparisons revealed reductions 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 reduced startle magnitude over this period. ANOVA revealed no significant effect of dose, a significant effect of time and a significant dose×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.

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 min, 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×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 (Fig. 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×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 (Fig. 2A) and startle magnitude (Fig. 2B) over the first 50 min of testing. ANOVA of PPI over this time period (Fig. 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×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 min of testing (Fig. 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×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 quinelorane on startle magnitude vs. PPI, dose subgroups were matched ($n=6$/dose) with nearly identical startle magnitudes during this initial 50-min period ($F<0.25$) (Fig. 3 (inset)). ANOVA of PPI in these rats confirmed a significant effect of quinelorane dose ($p<0.003$) (Fig. 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 quinelorane dose ($F<1$), time ($F=1.21$, *df* 4,84, NS) or dose×time interaction ($F=1.44$, *df* 8, 84, NS). Similarly, NOSTIM levels were unaffected by quinelorane 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.

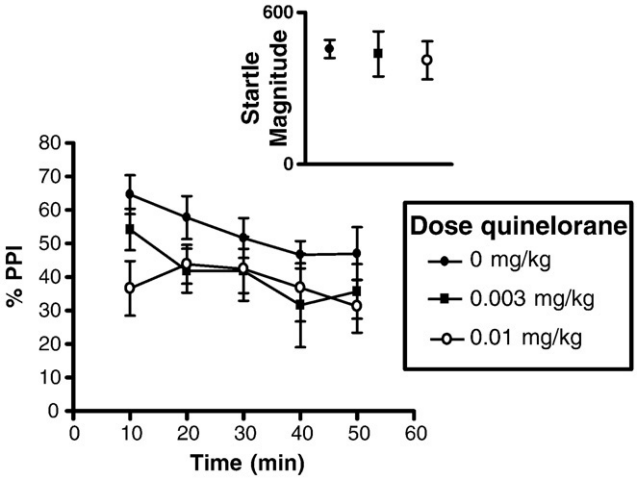

Fig. 3. Effects of quinelorane treatment on prepulse inhibition of acoustic startle after dose subgroups were matched for comparable startle magnitude (inset) during this initial 50-min period. ANOVA of PPI in these rats confirmed a significant effect of quinelorane dose. Post-hoc comparisons confirmed significant PPI-reducing effects of both 0.003-mg/kg and 0.01-mg/kg doses over this period.

4. Discussion

Systemic quinelorane 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) quinelorane-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, quinelorane-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 quinelorane 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 quinelorane, over a time period in which startle magnitude is both increased (10 min) and decreased (min 30–40) by this dose of quinelorane. Thus, quinelorane 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, quinelorane 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 quinelorane, 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 quinelorane 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 s.c. quinelorane injection, while PPI testing was delayed for 5 min 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 Fig. 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 min test. In one published report, PPI measured in a 240 min session (Zhang et al., 2000) declined over the initial 60 min 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 (Fig. 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).

Acknowledgements

Research was supported, in part, by grants from the National Institute on Alcohol Abuse and Alcoholism (AA014619) and National Institute of Drug Abuse (DA 019962) for LHP and DS, and the National Institute of Mental Health (MH68366) for NRS, YQ, MW. NRS has received support from Pfizer Pharmaceuticals (research funding) and Allergan Pharmaceuticals (research funding, consultancy funding). The authors are grateful for technical assistance provided by Dr. Richard Saint Marie, Ms. Shelley Breier and Mr. David Ko.

References

Bourdelais A, Kalivas PW. Apomorphine decreases extracellular GABA in the ventral pallidum of rats with 6-OHDA lesions in the nucleus accumbens. Brain Res 1992;577:306–11.
Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. Psychopharmacology (Berl) 2001;156:234–58.
Caille S, Parsons LH. SR141716A reduces the reinforcing properties of heroin but not heroin-induced increases in nucleus accumbens dopamine in rats. Eur J Neurosci 2003;18:3145–9.
Caille S, Parsons LH. Intravenous heroin self-administration decreases GABA efflux in the ventral pallidum: an in vivo microdialysis study in rats. Eur J Neurosci 2004;20:593–6.
Caille S, Parsons LH. Cannabinoid modulation of opiate reinforcement through the ventral striatopallidal pathway. Neuropsychopharmacology 2006;31:804–13.
Caine SB, Geyer MA, Swerdlow NR. Effects of D3/D2 dopamine receptor agonists and antagonists on prepulse inhibition of acoustic startle in the rat. Neuropsychopharmacology 1995;12:139–45.
Davis M, Gendelman DS, Tischler MD, Gendelman PM. A primary acoustic startle circuit: lesion and stimulation studies. J Neurosci 1982;2:791–805.
Hoffman HS, Ison JR. Reflex modification in the domain of startle: I. Some empirical findings and their implications for how the nervous system processes sensory input. Psychol Rev 1980;87:175–89.
Jones DL, Mogenson GJ. Nucleus accumbens to globus pallidus GABA projection subserving ambulatory activity. Am J Physiol 1980a;238:R65–69.
Jones DL, Mogenson GJ. Nucleus accumbens to globus pallidus GABA projection: electrophysiological and iontophoretic investigations. Brain Res 1980b;188:93–105.
Koch M, Schnitzler HU. The acoustic startle response in rats—circuits mediating evocation, inhibition and potentiation. Behav Brain Res 1997;89:35–49.
Kodsi MH, Swerdlow NR. Quinolinic acid lesions of the ventral striatum reduce sensorimotor gating of acoustic startle in rats. Brain Res 1994;643:59–65.
Kodsi MH, Swerdlow NR. Prepulse inhibition in the rat is regulated by ventral and caudodorsal striato-pallidal circuitry. Behav Neurosci 1995;109:912–28.
Kretschmer BD, Koch M. The ventral pallidum mediates disruption of prepulse inhibition of the acoustic startle response induced by dopamine agonists, but not by NMDA antagonists. Brain Res 1998;798:204–10.
Levant B. The dopamine D3 receptor: neurobiology and potential clinical relevance. Pharmacol Rev 1997;49:231–52.

Mogenson G, editor. Limbic-motor integration. New York: Academic press; 1987.
O'Dell LE, Manzardo AM, Polis I, Stouffer DG, Parsons LH. Biphasic alterations in serotonin-1B (5-HT1B) receptor function during abstinence from extended cocaine self-administration. J Neurochem 2006;99:1363–76.
O'Dell LE, Parsons LH. Serotonin1B receptors in the ventral tegmental area modulate cocaine-induced increases in nucleus accumbens dopamine levels. J Pharmacol Exp Ther 2004;311:711–9.
Paxinos GWC, editor. The rat brain in stereotaxic coordinates. San Diego: Academic Press; 1998.
Roberto M, Madamba SG, Stouffer DG, Parsons LH, Siggins GR. Increased GABA release in the central amygdala of ethanol-dependent rats. J Neurosci 2004a;24:10159–66.
Roberto M, Schweitzer P, Madamba SG, Stouffer DG, Parsons LH, Siggins GR. Acute and chronic ethanol alter glutamatergic transmission in rat central amygdala: an in vitro and in vivo analysis. J Neurosci 2004b;24:1594–603.
Ireland MD, Lowe AS, Reavill C, James MF, Leslie RA, Williams SC. Mapping the effects of the selective dopamine D2/D3 receptor agonist quinelorane using pharmacological magnetic resonance imaging. Neuroscience 2005;133:315–26.
Shafer RA, Levant B. The dopamine D3 receptor in cellular and organismal function. Psychopharmacology 1998;135:1–16.
Swerdlow NR, Braff DL, Geyer MA. GABAergic projection from nucleus accumbens to ventral pallidum mediates dopamine-induced sensorimotor gating deficits of acoustic startle in rats. Brain Res 1990;532:146–50.
Swerdlow NR, Geyer MA, Braff DL. Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. Psychopharmacology (Berl) 2001;156:194–215.
Varty GB, Higgins GA. Dopamine agonist-induced hypothermia and disruption of prepulse inhibition: evidence for a role of D3 receptors? Behav Pharmacol 1998;9:445–55.
Wan FJ, Geyer MA, Swerdlow NR. Accumbens D2 modulation of sensorimotor gating in rats: assessing anatomical localization. Pharmacol Biochem Behav 1994;49:155–63.
Zhang J, Forkstam C, Engel JA, Svensson L. Role of dopamine in prepulse inhibition of acoustic startle. Psychopharmacology 2000;149:181–8.