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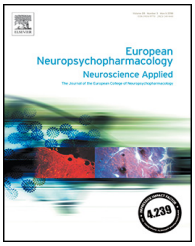

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SHORT COMMUNICATION

Acute and subchronic PCP attenuate D2 autoreceptor signaling in substantia nigra dopamine neurons

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Abstract
Phencyclidine (PCP) administration is commonly used to model schizophrenia in laboratory animals. While PCP is well-characterized as an antagonist of glutamate-sensitive N-methyl-D-aspartate (NMDA) receptors, its effects on dopamine signaling are not well understood. Here we used whole-cell and cell-attached patch-clamp electrophysiology of substantia nigra dopamine neurons to determine the effects of acute and subchronic PCP exposure on both dopamine D2 autoreceptor-mediated currents and burst firing evoked by glutamate receptor activation. Acute PCP affected D2 autoreceptor-mediated currents through two apparently distinct mechanisms: a low-concentration dopamine transporter (DAT) inhibition and a high-concentration potassium (GIRK) channel inhibition. Subchronic administration of PCP (5 mg/kg, i.p., every 12 h for 7 days) decreased sensitivity to low dopamine concentrations, and also enhanced evoked burst firing of dopamine neurons. These findings suggest the effects of PCP on dopaminergic signaling in the midbrain could enhance burst firing and contribute to the development of schizophreniform behavior.

1. Introduction

Subchronic administration of the abused substance and N-methyl-D-aspartate (NMDA) receptor antagonist phen-

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cyclidine (PCP) is commonly used in rodents to model the putative hypoglutamatergic state observed with schizophrenia (Castane et al., 2015). The effects of subchronic PCP are also consistent with findings in humans that repeated abuse of PCP induces schizophreniform symptoms and hyperresponsivity of the mesolimbic dopamine system (Jentsch et al., 1999). The well-characterized antagonism of excitatory NMDA receptors by PCP is difficult to reconcile with observed increases in midbrain dopamine neuron activity. However, PCP may also disrupt inhibitory neurotransmission. Dopamine neurons express D2 autoreceptors on their cell bodies and dendrites that couple to G protein-coupled, inwardly-rectifying potassium (GIRK) channels that hyperpolarize the cell (Beckstead et al., 2004; Lacey et al., 1987; Robinson et al., 2017). Repeated activation of D2 autoreceptors induces long-term depression of inhibitory input and increases dopamine neuron activity (Beckstead and Williams, 2007; Piccart et al., 2015). *In vitro*, PCP has been reported to display agonist action of D2 receptors in their high-affinity state (Kapur and Seeman, 2002; Seeman and Guan, 2008; Seeman et al., 2005), to inhibit the dopamine uptake transporter (DAT; Schiffer et al., 2003), and to inhibit GIRK channel signaling (Kobayashi et al., 2011). However, binding assays have revealed no affinity of three PCP analogues for either the D2 receptor or DAT (Roth et al., 2013) and no stimulatory agonist action for PCP at D2 receptors (Odagaki and Toyoshima, 2006). Thus, the underlying action of PCP on dopamine signaling remains unclear.

Here we used electrophysiological recordings of substantia nigra dopamine neurons in brain slices from adult mice to determine which putative effects of PCP alter dopaminergic signaling. We hypothesized that blockade of DAT or GIRK channels, and/or direct agonist action at D2 autoreceptors by acute or subchronic PCP could depress inhibition of midbrain dopamine neurons and enhance firing activity, in agreement with the hyperdopaminergic state observed in schizophrenia and schizophrenia models. The results indicate a role for altered dopaminergic signaling in subchronic PCP models.

2. Experimental procedures

2.1. Animals

Male DBA/2J mice (Jackson Laboratory) were group-housed on a reverse cycle (lights off 0900–1900), with food and water available ad libitum. Treated mice received PCP (5 mg/kg, i.p.) or saline every 12 h for 7 consecutive days, followed by 7 days with no treatment. All experiments were reviewed and approved by the UT Health, San Antonio Institutional Animal Care and Use Committee.

2.2. Brain slice electrophysiology

Brain slicing and electrophysiological procedures are described in the supplementary material. In cells from naive animals, we elicited D2 autoreceptor-mediated currents by iontophoresis of dopamine (1 M in the pipette). Dopamine was retained with negative current and ejected as a cation with 50–200 ms pulses of +150–220 nA using an ION-100 iontophoresis generator (Dagan). In cells from treated mice, maximal responses to dopamine were elicited with 5 s iontophoretic pulses spaced 5 min apart. After another 5 min, dopamine (3 μM, then 10 μM) was then bath perfused. Percent effect was calculated as the peak current amplitude in response to dopamine divided by the maximal current amplitude in response to the first iontophoretic pulse, x 100%. $GABA_B$ receptor-mediated currents were also elicited, using iontophoresis of GABA (1 M, pH 4.0). Finally, dopamine neuron burst firing was induced by iontophoresis of D-aspartic acid (800 mM, ejected for 50–200 ms as an anion with a negative pulse) as previously reported (Branch et al., 2013).

2.3. Drugs

Kynurenic acid and MK-801 (for slicing), PCP, and dopamine hydrochloride were purchased from Sigma-Aldrich (St-Louis, USA).

2.4. Statistical analyses

Data were collected using Axograph 1.3.5 (Axograph Scientific) and LabChart (AD Instruments). Two-way (RM) analyses of variance (ANOVAs) or paired Student's *t*-tests were used for between-group comparisons. Tukey's or Sidak's post hoc tests were performed subsequent to significant ANOVAs. Data are presented as mean ± SEM; α was set *a priori* at 0.05. Asterisks in the figures refer to posthoc tests, except for the vertical bar in panel 2E which is a significant main effect. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$.

3. Results

3.1. Acute PCP decreases D2 current amplitude

To determine whether PCP affects dopamine cell function we obtained whole-cell voltage clamp (−60 mV) recordings of dopamine neurons from naive mice and bath perfused PCP. Most cells exhibited a slight outward shift in holding current in response to PCP (Fig. 1A; $n = 19$ pooled cells), but it did not vary across concentration (0.3–10 μM; inset). To determine the effects of PCP on dopamine signaling we measured D2 autoreceptor, GIRK channel-mediated currents that were elicited by a once-per-minute iontophoresis of dopamine. PCP (0.3–10 μM) was applied to the bath for 5 min (Fig. 1B) and the change in peak current amplitude measured (Fig. 1C). Middle and high concentrations of PCP depressed current amplitudes, measured as the percent reduction from baseline in peak current amplitude immediately following PCP (1 μM [$n = 13$]: 12.84 ± 3.21%, 3 μM [$n = 6$]: 21.73 ± 4.08%, 10 μM [$n = 9$]: 78.20 ± 2.19%), but not in response to the lowest concentration (300 nM [$n = 7$], −4.36 ± 1.9%, Fig. 1D). Two-way RM ANOVA revealed a main effect of concentration ($F_{3,31} = 120.4$, $p < 0.0001$), with significantly larger depression in response to 1, 3, and 10 μM compared to 300 nM ($p < 0.01$, $p < 0.001$ and $p < 0.0001$ respectively), and significantly larger depression in response to 10 μM compared to 1 and 3 μM ($p < 0.0001$). Prolonged effects of PCP, measured as the average % reduction in peak current amplitude between minutes 35–40, were observed at the highest concentration (10 μM: 40.96 ± 8.55% reduction), but not the lower concentrations (300 nM: −8.95 ± 3.9% reduction, 1 μM: 0.11 ± 5.23% reduction, 3 μM: 2.73 ± 12% reduction; Fig. 1E). Two-way RM ANOVA

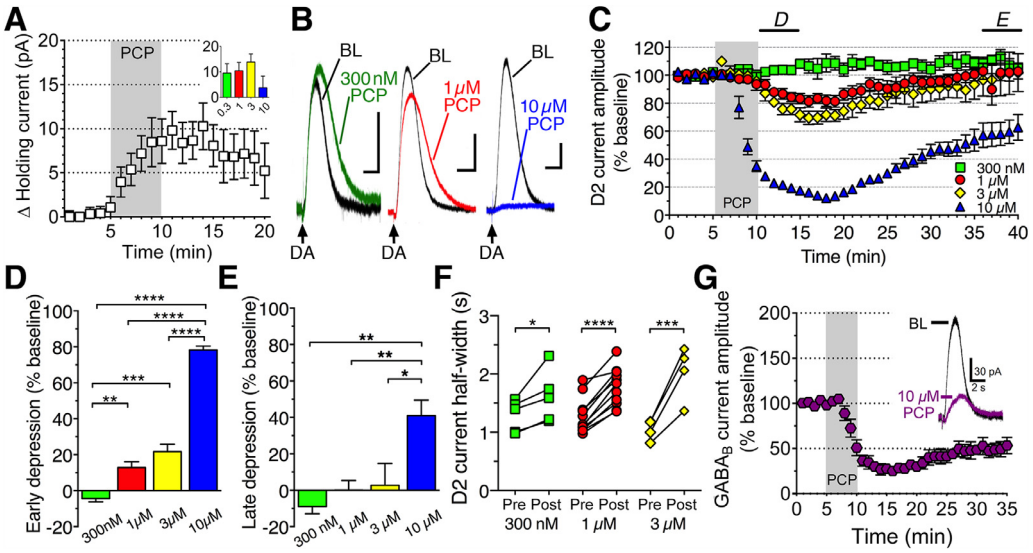

Fig. 1 Acute PCP inhibits DAT and GIRK channel-mediated currents in dopamine neurons. A) PCP (0.3–10 μM) bath perfusion produced a small outward current (pooled data shown) that did not appear to be concentration-dependent (inset). **B)** Sample traces depicting effects of PCP (0.3–10 μM) on D2 autoreceptor currents induced by dopamine iontophoresis (DA, arrows): baseline (BL) and after PCP (0.3–10 μM). Scale bars: 1 s, 50 pA. **C)** Time course of PCP effects on D2 autoreceptor-mediated current amplitudes. Horizontal bars: time points analyzed in panels *D* and *E*. **D)** PCP-induced early depression of D2 autoreceptor-mediated currents. **E)** PCP-induced late depression of D2 autoreceptor-mediated currents. **F)** PCP (0.3–3 μM) prolonged D2 receptor current half-widths. **G)** 10 μM PCP inhibited $GABA_B$ receptor-, GIRK channel-mediated current amplitudes (sample trace, inset).

indicated a main effect of concentration on sustained depression ($F_{3,25} = 7.64$, $p = 0.0009$), with significantly larger depression in response to 10 μM compared to 300 nM, 1 μM, and 3 μM ($p < 0.01$, $p < 0.01$ and $p < 0.05$ respectively). Moreover, PCP increased the half-width of dopamine currents in every cell recorded (Fig. 1F), but this could not be reliably measured for 10 μM PCP due to severely reduced current amplitudes. To determine if PCP effects generalized to other GIRK channel-mediated currents, we also elicited $GABA_B$ receptor-, GIRK channel-mediated currents with iontophoresis of GABA. We observed a similar decrease in current amplitudes in response to 10 μM PCP ($n = 4$; Fig. 1G). Taken together, the data are consistent with two acute effects of PCP: a mild decrease in dopamine uptake at low concentrations, and an inhibition of GIRK channel signaling at higher concentrations.

3.2. Subchronic PCP decreases D2 autoreceptor sensitivity

To determine the effects of repeated exposure of PCP on D2 autoreceptor currents, we next patch clamped dopamine neurons from mice that had been treated for seven days with either PCP (5 mg/kg, twice daily) or saline. We first applied two 5 s iontophoretic pulses of dopamine at a 5-min interval, followed another 5 min thereafter by 5-min bath applications of 3 μM and then 10 μM dopamine (Fig. 2A). We observed no significant difference between cells from PCP- ($n = 12$) and saline-treated ($n = 8$) mice in maximal peak currents in response to iontophoresis of dopamine (main effect of treatment: $F_{1,28} = 0.0055$, $p = 0.94$, Fig. 2B), or in the decrease observed in peak current amplitude on the second application (main effect of application: $F_{1,28} = 64.2$, $p < 0.0001$, interaction: $F_{1,28} = 1.224$, $p = 0.28$, Fig. 2B). We did observe a PCP-induced decrease in D2 autoreceptor sensitivity, measured as the current produced by 3 and 10 μM dopamine normalized to the first iontophoretic application (main effect of treatment: $F_{1,18} = 7.37$, $p = 0.014$, main effect of time: $F_{9,162} = 14.69$, $p < 0.0001$, interaction: $F_{9,162} = 3.78$, $p = 0.0002$, Fig. 2C).

3.3. Subchronic PCP enhances dopaminergic burst firing

Midbrain dopamine neurons fire bursts of action potentials in response to glutamate input (Overton and Clark, 1997). To test whether decreased auto-inhibition in dopamine neurons from PCP-treated mice could enhance burst firing, we next simulated the effects of glutamate input to dopamine neurons through iontophoresis of D-aspartic acid. In order to "qualify" for further recording we first required the cell to fire a minimum of 4 spikes in response to a 100 ms iontophoretic pulse. We then tested a range of pulse durations (50–200 ms). Bursts were identified by ≥1 interspike interval <80 ms, as previously described (Branch et al., 2013; Grace and Bunney, 1984). Dopamine neurons from PCP-treated mice exhibited a large proportion of cells that burst in response to 100 ms iontophoresis (18/24, 75%), in comparison to a much smaller portion of cells from saline-treated littermates (9/25, 36%). Moreover, only 5/24 (20.8%) of the cells recorded from PCP-treated animals did not "qualify," compared to 14/25 (56%) of the cells from saline-treated mice (Fig. 2D). Analysis performed specifically on the cells

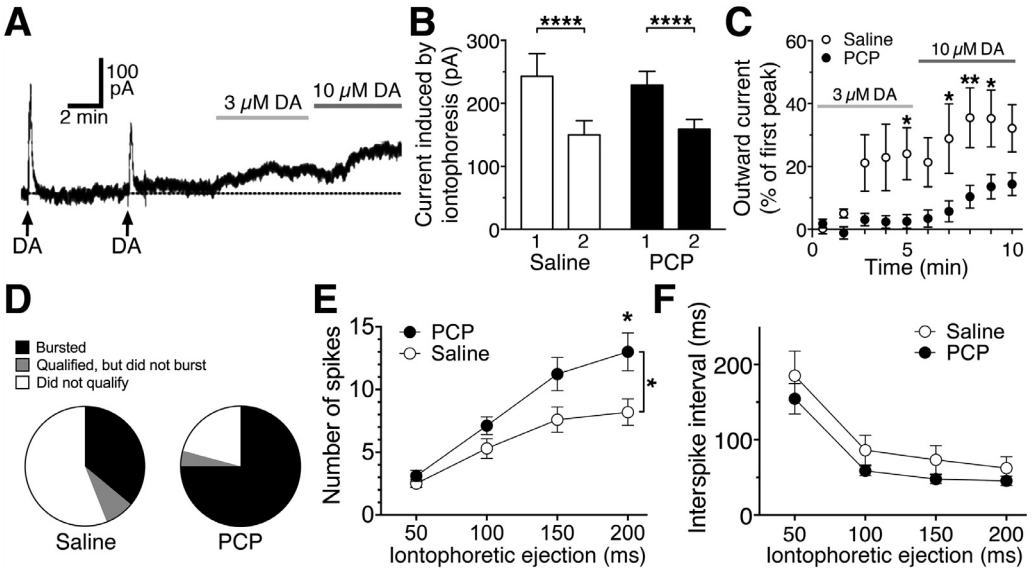

Fig. 2 Subchronic PCP affects dopamine neuron excitability. A) Sample trace from a saline-treated mouse depicting experimental protocol: two maximal iontophoretic pulses (5 s, arrows) separated by 5 min, followed by bath perfusion of 3 and 10 μM dopamine (DA). **B)** Subchronic PCP treatment did not affect maximal current amplitude or the decrease in current amplitude observed with the second iontophoretic pulse. **C)** Subchronic PCP treatment attenuated currents mediated by bath perfusion of 3-10 μM dopamine. **D)** Neurons from PCP-treated animals were more prone to bursting (75% burst, 4% qualified but did not burst, and 21% did not qualify) in response to a 100 ms pulse of D-aspartic acid, compared to cells from saline-treated littermates (36% burst, 8% qualified but did not burst, 56% did not qualify). **E)** Subchronic PCP treatment increased the number of spikes per burst compared to saline treatment. **F)** Subchronic PCP treatment did not alter interspike intervals compared to cells from saline-treated littermates.

that did burst indicated enhanced firing in PCP-treated mice. Two-way RM ANOVA indicated a significant increase in number of spikes in cells from PCP- ($n = 17$) versus saline - ($n = 10$) treated mice ($F_{1,25} = 4.23$, $p = 0.0498$; Fig. 2E). There were also significant effects of iontophoretic pulse duration ($F_{3,75} = 53.22$, $p < 0.0001$) and an interaction between treatment and pulse duration ($F_{3,75} = 3.77$, $p = 0.01$, Fig. 2E). Analysis of the shortest interspike interval showed no effect of treatment ($F_{1,25} = 1.91$, $p = 0.18$; Fig. 2F), a significant effect of iontophoretic pulse duration ($F_{3,75} = 46.75$, $p < 0.0001$), and no interaction ($F_{3,75} = 0.14$, $p = 0.93$).

4. Discussion

Interactions between PCP and dopamine D2 receptors have been reported (Balla et al., 2003; Gleason and Shannon, 1997; Kapur and Seeman, 2002; Seeman et al., 2005), but the effects of PCP treatment on dopaminergic signaling in midbrain neurons have not been studied. Here, we investigated the effects of both acute PCP application and subchronic PCP treatment on D2 autoreceptor-mediated currents in substantia nigra dopamine neurons in mouse brain slices.

Acute application of PCP to brain slices from naive mice produced two effects. First, PCP (0.3-3 μM) produced a modest but clear widening of dopamine currents consistent with DAT inhibition (Beckstead et al., 2004). This is consistent with a previously published PET study indicating an interaction between PCP and the cocaine binding site, suggesting possible DAT blockade (Schiffer et al., 2003). This was the only effect observed at 300 nM and actually caused a slight increase in current amplitudes. We went on to reproduce this effect in a separate experiment using electrically-evoked D2 receptor inhibitory postsynaptic currents (Supplementary Fig. S1; Beckstead et al., 2004). Second, PCP (1-10 μM) also generally inhibited GIRK channel-mediated currents. Bath perfusion of PCP robustly inhibited D2 receptor currents, consistent with previous reports of increased dopamine neuron firing rates and bursting by PCP administered *in vivo* (French et al., 1993; Svensson et al., 1995). However, this experiment did not distinguish between direct effects at the D2 receptor and those at the GIRK channel. We therefore also used iontophoresis to activate $GABA_B$ receptors, which couple to a GIRK conductance that partially overlaps with the one activated by D2 autoreceptors (Beckstead and Williams, 2007). Despite the fact that we had hypothesized PCP agonism at D2 receptors, PCP (10 μM)-induced inhibition of $GABA_B$ currents appeared nearly identical to inhibition of D2 currents, strongly suggesting GIRK channels as the locus of effect. One previous study showed that PCP inhibits GIRK channels expressed in *Xenopus laevis* oocytes (Kobayashi et al., 2011). Interestingly, those effects were only observed at higher concentrations, suggesting that GIRK channel signaling in dopamine neurons is more sensitive to PCP than in an expression system.

Subchronic PCP treatment is commonly used to model schizophrenia in animals (Castane et al., 2015). D2 autoreceptors provide crucial inhibition of midbrain dopamine neuron firing and downstream dopamine release in the

striatum, which is enhanced in schizophrenia (Howes et al., 2012). Attenuated D2 autoreceptor function could therefore contribute to schizophreniform behaviors seen in PCP-treated animals. Indeed, we observed that subchronic PCP treatment decreased D2 autoreceptor-mediated currents, evidenced by an attenuated response to sub-maximal concentrations of dopamine. We did not, however, observe an effect of treatment on maximal currents. Although multiple possible explanations exist, the decrease in D2 signaling may be caused by decreased coupling efficiency between D2 receptors and GIRK channels, which can be overcome with maximal concentrations of dopamine. Indeed, many psychoactive drugs modulate expression of regulator of G-protein signaling proteins (Lomazzi et al., 2008) which in turn regulate G-protein coupling to GIRK channels. Alternatively, a decrease in $GABA_B$-GIRK signaling has been noted subsequent to antagonism of NMDA receptors (Workman et al., 2015). However, further investigation is necessary.

We next hypothesized that attenuated inhibition would enhance burst firing of midbrain dopamine neurons. Indeed, dopamine cells from PCP-treated mice exhibited enhanced burst firing; a larger proportion of cells burst and fired more spikes per burst in response to aspartate iontophoresis. This is in agreement with an earlier report from our lab that showed enhanced burst firing in food-restricted animals that was affected by D2 autoreceptor availability (Branch et al., 2013). However, complementary mechanisms could also contribute to enhanced burst firing. For instance, increased expression of the NR1 NMDA receptor subunit has been observed in the substantia nigra of schizophrenic patients (Mueller et al., 2004). This subunit is critical to the generation of bursts in dopamine neurons (Zweifel et al., 2009), therefore if PCP produces a similar effect it could possibly enhance burst firing as well.

In summary, these results indicate that both acute and subchronic PCP decrease D2 autoreceptor signaling, which could produce some of the schizophreniform behaviors observed in PCP-treated mice. The effects of PCP on the NMDA receptor are well-established. However, the demonstration of PCP effects on D2 autoreceptor signaling in the substantia nigra adds to our knowledge of acute drug mechanisms and may aid in the interpretation of interventional studies that use this model.

Contributors

EP and MJB designed the study. EP, CWT, and MJB performed experiments and analyzed the data. EP wrote the manuscript, which was edited by CWT and MJB. All authors approved submission of the final manuscript.

Conflict of interest

The authors declare no potential conflicts.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2019.01.108.

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