Rapid Communication

Dual 5-HT_3 and 5-HT_6 Receptor Antagonist FPPQ Normalizes Phencyclidine-Induced Disruption of Brain Oscillatory Activity in Rats

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Abstract

Schizophrenia is a severe mental disorder featuring psychotic, depressive, and cognitive alterations. Current antipsychotic drugs preferentially target dopamine D_2-R and/or serotonergic 5-HT_2A/1A-R. They partly alleviate psychotic symptoms but fail to treat negative symptoms and cognitive deficits. Here we report on the putative antipsychotic activity of (1-[(3-fluorophenyl)sulfonyl]-4-(piperazin-1-yl)-1H-pyrrolo[3,2-c]quinoline dihydrochloride) (FPPQ), a dual serotonin 5-HT_3-R/5-HT_6-R antagonist endowed with pro-cognitive properties. FPPQ fully reversed phencyclidine-induced decrease of low-frequency oscillations in the medial prefrontal cortex of anaesthetized rats, a fingerprint of antipsychotic activity. This effect was mimicked by the combined administration of the 5-HT_3-R and 5-HT_6-R antagonists ondansetron and SB-399 885, respectively, but not by either drug alone. In freely moving rats, FPPQ countered phencyclidine-induced hyperlocomotion and augmentation of gamma and high-frequency oscillations in medial prefrontal cortex, dorsal hippocampus, and nucleus accumbens. Overall, this supports that simultaneous blockade of 5-HT_3-R and 5-HT_6-R-like that induced by FPPQ-can be a new target in antipsychotic drug development.

Keywords: Schizophrenia, NMDA-R antagonists, 5-HT_3-R, 5-HT_6-R, antipsychotics
Introduction

Schizophrenia is a chronic and highly disruptive psychiatric disorder characterized by the presence of positive and negative symptoms and an important cognitive decline. Available drugs are partly effective for positive symptoms but fail in treating negative/cognitive symptomatology (Leucht et al., 2013). First- and second-generation antipsychotic drugs preferentially antagonize dopamine D₂-R and serotonin 5-HT₁A-R, respectively. A third generation of drugs showing partial agonism at D₂-R and 5-HT₁A-R together with 5-HT₂A-R antagonism has also been developed (Newman-Tancredi and Kleven, 2011). Despite new improvements, difficulties for an adequate treatment of schizophrenia persist. Novel strategies targeting the glutamatergic system, including mGluR2/3-R agonists, failed despite initial expectations (Adams et al., 2014; Bugarski-Kirola et al., 2017).

Recently, Zajdel et al. (2021) proposed a novel mechanism to achieve antipsychotic and pro-cognitive properties by a non-dopaminergic action. Based on evidence that 5-HT₁A-R and 5-HT₂A-R antagonists improve cognition when administered as adjuvant therapy to antipsychotics, they developed and tested a dual-acting 5-HT₁A-R/5-HT₂A-R antagonist, FPPQ (1-[(3-fluorophenyl)sulfonyl]-4-(piiperazin-1-yl)-1H-pyrrolo[3,2-c]quinoline dihydrochloride). The simultaneous blockade of 5-HT₁A-R, 5-HT₂A-R by FPPQ dose-dependently prevented phencyclidine (PCP)-induced short-term memory deficits in the novel object recognition test (NORT) and reversed PCP-induced hyperlocomotion.

PCP showed to activate thalamo-cortical circuits through a preferential blockade of NMDA-R in the reticular nucleus of the thalamus (Santana et al., 2011; Troyano-Rodriguez et al., 2014). This nucleus is composed exclusively of GABA neurons that tonically inhibit the rest of thalamic nuclei. In parallel with enhancing the activity of principal neurons in thalamo-cortical areas, PCP markedly reduced the power of low-frequency oscillations (LFO; 0.15–4 Hz) in the medial prefrontal cortex (mPFC) of anesthetized rats. All antipsychotic drugs tested so far, irrespective of their pharmacological profile, reverse the decrease in LFO induced by PCP (Kargieman et al., 2007; Lladó-Pelfort et al., 2016). In anaesthetized rats, the power of LFO (0.15–4 Hz) was calculated for the last 2-minute period before PCP or drug administration and stored at −20°C until used. FPPQ (Zajdel et al., 2021) solutions were prepared daily in saline (i.v.), and in hydroxyl-propyl-β-cyclodextrin 10%+ glucose monohydrate 4.4% adjusted to pH 6–6.5 with NaOH 1M (i.p.). FPPQ was discovered by the scientific consortium of the Faculty of Pharmacy Jagiellonian University Medical College, University of Montpellier, and Institute of Pharmacology Polish Academy of Sciences (Zajdel et al., 2015) and licensed to Spherium Biomed (Barcelona, Spain). SB-399 885 (Sigma/RBI) solutions were prepared freshly in 1% Tween 80 (i.v.). Buprenorfine (Buprex®) and enrofloxacin (Enrovet®) were dissolved in saline. Doses are expressed as free base. All compounds were administrated in a final volume of 0.25–2 mL/kg.

In Vivo Electrophysiology in Anaesthetized Rats

PCP (0.25–0.5 mg/kg), OND (1.28 mg/kg), SB-399 885 (10 mg/kg), and FPPQ (3 mg/kg) were administered i.v. Rats were anesthetized with chloral hydrate (induction: 400 mg/kg i.p.; maintenance: 50–70 mg/kg/h). Local field potentials were recorded in mPFC (coordinates AP +3.4, L-0.7, DV-2.8 from bregma and skull; Paxinos and Watson, 2005) as previously described (Kargieman et al., 2007). After recording stable baseline activity (5 minutes), 1 or 2 doses of PCP were administered. After 2 minutes of stable PCP effect, FPPQ, OND, SB-399 885, or the combination of the latter 2 drugs were slowly administrated. Recordings were kept for 10 minutes after drug administration.

Simultaneous Recordings and Locomotor Activity Measures in Freely Moving Rats

Rats were implanted with Plastics One electrodes (Roanoke, VA, USA) under isoflurane anesthesia (induction: 5%; maintenance: 1.5%–2%) as previously described (Riga et al., 2017). Animals were pretreated (30 minutes before anesthesia) with an analgesic (buprenorfine 0.05 mg/kg, s.c.). Recording electrodes were implanted at mPFC (AP +3.2, L-0.5, DV-2.8) and dorsal hippocampus (dHPC; AP-1.5, L-0.7, DV-2.1) (coordinates from bregma and skull; Paxinos and Watson, 2005). A ground screw (AP-8.7 L +.4) and 3 stabilizer screws were also implanted. Buprenorfine (0.05 mg/kg s.c.) and a prophylactic antibiotic (enrofloxacin 7.5 mg/kg s.c.) were given during 3 days after surgery.

Local field potential recordings were performed in a 40 × 40 cm open field using a digital Lynx system and Cheetah software (Neuralynx, Westlake Village, CA, USA). The signal was obtained at 3.2 kHz sampling rate and filtered between 0.1 and 200 Hz. All recordings were subsequently down sampled 10 times before analysis. Simultaneously, locomotor activity was recorded during electrophysiological recordings and analyzed offline by the SMART video-tracking software (Harvard-Panlab, Barcelona, Spain).

Recordings were performed 1 week after surgery. On the recording day, after 20 minutes of baseline recording, FPPQ (or vehicle [VEH]) and PCP were injected 45 minutes apart, and recordings were performed for 45 minutes after last injection.

Finally, rats were killed by an anesthetic overdose, and the histological localization of electrodes was performed.

Data and Statistical Analyses

In anaesthetized rats, the power of LFO (0.15–4 Hz) was calculated for the last 2-minute period before PCP or drug administration and in 3 consecutive 2-minute periods before the end...
of recording (see below). Recordings were analyzed off-line with Spike2 software using built-in and self-developed scripts. Mean LFO power was quantified by averaging 6 consecutive 10-second periods (for each minute) and then generating the mean of 2 minutes. Fast Fourier Transformation with a resolution of 0.15 Hz was used. LFO power is expressed as $\mu V^2$.

For recordings in freely moving rats, raw data were imported to MatLab environment (MathWorks, MA, USA) for off-line power wavelet analysis using built-in and self-developed routines. The frequency bands analyzed were delta (0.2–4 Hz), theta (4–10 Hz), beta (10–30 Hz), gamma (30–80 Hz), and HFO (140–180 Hz). Data were averaged in 5-minute periods. Injection periods (5 minutes post-drug administrations) were excluded from analysis. Data were expressed as percentage of basal values in each time period. One- or 2-way ANOVA (with treatment and time factors) were performed, followed by Duncan’s tests for post-hoc analysis, as appropriate. Locomotor activity data were analyzed by Mann-Whitney test. Data are shown as means ± SEM. Statistical analysis was conducted by using GraphPad Prism version 6. Statistical significance has been set at the 95% confidence level (two-tailed).

RESULTS

Concurrent 5-HT$_3$R and 5-HT$_6$R Receptor Blockade Reverses PCP-Induced Decrease of LFO in mPFC

PCP administration induced a dramatic decrease of LFO in the mPFC of anesthetized rats. Given the capacity of FPPQ to attenuate PCP-induced hyperactivity and recognition memory deficits (Zajdel et al., 2021), we examined its ability as well as that of OND (5-HT$_6$R antagonist) and SB-399 885 (5-HT$_7$R antagonist) to reverse PCP effects on LFO.

FPPQ fully reversed the PCP-induced decrease in mPFC LFO (Fig. 1A,E), similarly to atypical antipsychotics (Fig. 1K, modiﬁed from Lladó-Pelfort et al., 2016). In contrast, OND (Fig. 1B,F) and SB-399 885 (Fig. 1C,G,I) failed to reverse the PCP-induced disruption of LFO in mPFC. Interestingly, the combination of both drugs (OND + SB-399 885) fully countered PCP effects on LFO (Fig. 1D,H,J), mimicking the effect of FPPQ. Figure 1A–D shows representative examples of the ability of these drugs to reverse the PCP-induced loss of LFO in mPFC (see statistical analyses in legend to Fig. 1).

FPPQ Pretreatment Prevents PCP-Induced Alterations in Brain Oscillations and Hyperlocomotion in Freely Moving Rats

Acute FPPQ treatment did not evoke major changes on brain oscillatory activity in the mPFC, NAc, and dHPC of freely moving rats. No differences between VEH- and FPPQ-pretreated values (from 25 to 65 minutes) were found in any case (Fig. 2A–C). PCP administration increased the power of beta, gamma, and HFO bands in the mPFC of VEH-treated rats (n = 5) (Fig. 2A). Moreover, PCP enhanced theta, beta, and HFO oscillations in NAc (Fig. 2B) and gamma and HFO in dHPC (Fig. 2C) (n = 6 for each area). PCP-induced changes in mPFC theta and NAc delta bands were also found. Significant differences between basal and PCP values in the VEH + PCP group were found at different time points. Remarkably, FPPQ pretreatment avoided all PCP-induced effects on oscillatory activity in freely moving rats except on the HFO band in dHPC (n = 5 for each area). Significant differences between the VEH + PCP and FPPQ + PCP groups were found in all cases but at different times (see statistical analyses in legend to Fig. 2).

In parallel, PCP administration signiﬁcantly increased locomotor activity in VEH-pretreated rats (VEH + PCP; n = 6) as shown by the increased distance moved in the open field and the movement pattern representations (Fig. 2D). This effect was markedly attenuated in FPPQ-pretreated rats (FPPQ + PCP; n = 5) (*P < .05; Mann Whitney test).

Discussion

The present work shows that the dual 5-HT$_3$R/5-HT$_6$R antagonist FPPQ reverses or prevents PCP-induced alterations of mPFC LFO and brain oscillatory activity. Both effects are predictive of potential clinical antipsychotic activity. Interestingly, antipsychotic effects appear to depend on the simultaneous blockade of 5-HT$_3$R and 5-HT$_7$-R.

As observed for first- and second-generation antipsychotics, including DA D$_2$-R blockers and preferential 5-HT$_7$R antagonists, FPPQ markedly reduced PCP-induced hyperlocomotion (Kargieman et al., 2007; Santana et al., 2011) after the preferential blockade of NMDA-R in GABAergic neurons of the reticular thalamic nucleus (Troyano-Rodriguez et al., 2014). Interestingly, first- and second-generation antipsychotic drugs, with varying affinities for D$_3$-R and 5-HT$_7$R, together with new agents also acting at 5-HT$_3$R, reverse the decrease in LFO induced by PCP, making this reversal a fingerprint of potential clinical antipsychotic action (Kargieman et al., 2007; Lladó-Pelfort et al., 2016; Van den Munkhof et al., 2017).

Remarkably, the reversal by FPPQ appears to depend on the concurrent additive or synergistic blockade of 5-HT$_3$R and 5-HT$_6$R, since the respective antagonists OND and SB-399 885 failed to induce any significant change when administered alone but fully reversed PCP effects when administered together. The exact mechanism(s) responsible for this effect are unknown but may depend on the expression of 5-HT$_3$R and 5-HT$_6$R in brain elements involved in the control of oscillatory activity. Hence, in addition to the medullary nuclei involved in motor control, such as the area postrema, 5-HT$_7$R are exclusively located in GABAergic interneurons of the neocortex and the hippocampal formation (Morales and Bloom, 1997; Puig et al., 2004). In the neocortex, 5-HT$_6$R-expressing GABA interneurons represent the largest population of GABA interneurons in upper layers (Puig et al., 2004; Santana and Artigas, 2017). The physiological stimulation of the serotonergic raphe nuclei evokes fast ionotropic excitatory responses in GABA cells expressing 5-HT$_3$R in the mPFC (Puig et al., 2004) and hippocampus (Varga et al., 2009), respectively. Despite their preferential localization in layers I–III, 5-HT$_6$R-expressing GABA interneurons tightly control the activity of layer V neurons projecting to subcortical structures, such as the midbrain monoamine nuclei (Santana and Artigas, 2017). Hence, the administration of the selective 5-HT$_3$R antagonist OND or the antidepressant drug vortioxetine (also blocking 5-HT$_6$R with high affinity) increased the discharge rate of approximately 70% of midbrain-projecting layer V pyramidal neurons in rat mPFC (Riga et al., 2016). A large population of pyramidal neurons in layer V of the same mPFC areas also project to dorsal and ventral striatum (caudate-putamen and NAc) (Gabbott et al., 2005), which show the highest density of 5-HT$_7$R in rat brain (Helboe et al., 2015). Therefore, although not tested experimentally, it is possible that GABA cells expressing 5-HT$_7$R...
also control the activity of layer V pyramidal neurons projecting to caudate-putamen and NAc. Hence, 5-HT$_3$-R blockade would increase the cortical excitatory input onto medium-size spiny GABAergic striatal neurons expressing 5-HT$_6$-R. The simultaneous blockade of both receptors would then affect nerve transmission in cognitive and affective basal ganglia circuits, which feed back to the neocortex via the thalamus, thus attenuating the increased thalamo-cortical activity induced by PCP.

Additionally, 5-HT$_6$-R are located in a much lower density in the neocortex and HPC, where they are expressed in pyramidal neurons and in 15% of GABAergic interneurons, most of which also express 5-HT$_3$-R (Helboe et al., 2015). This regional and cellular localization represents an additional level of interaction between both receptors, which may add to the above-mentioned control of basal ganglia circuits.

Interestingly, without altering oscillatory activity by itself, FPPQ was also able to prevent the increase in the power of various oscillatory bands evoked by PCP in the 3 forebrain areas examined (mPFC, NAc, and dHPC), where 5-HT$_3$-R and 5-HT$_6$-R are expressed. In the PFC, PCP moderately increased the power of theta and beta oscillations and markedly increased gamma and HFO powers. FPPQ pretreatment fully prevented PCP effect on theta, beta, and HFO and markedly attenuated the gamma elevation. In NAc, PCP significantly increased the power of theta, beta, and HFO, an effect fully prevented by FPPQ in all frequency bands. Likewise, in dHPC, PCP evoked a moderate yet non-significant decrease of the delta band and markedly increased the power of the gamma and high-frequency bands, both effects significantly attenuated by FPPQ pretreatment. These effects agree with previous data indicating an increase of gamma oscillations by NMDA-R antagonists, including PCP (Hakami et al. 2009; Jones et al., 2012), an effect partly antagonized by antipsychotic drugs, which by themselves reduced gamma power (Jones et al., 2012).

Recently, Zajdel et al. (2021) found that FPPQ dose-dependently prevented PCP-induced short-term memory deficits in the NORT. The effects of FPPQ were similar to those produced by the 5-HT$_3$-R antagonist ondansetron. In this experiment, there is compelling evidence that the blockade of 5-HT$_3$-R by OND also produces pro-cognitive effects in preclinical and clinical trials.
Figure 2. Oscillatory activity in (A) the medial prefrontal cortex (mPFC), (B) nucleus accumbens (NAc), and (C) dorsal hippocampus (dHPC) was measured after PCP administration (5 mg/kg) in vehicle (VEH) and FPPQ (3 mg/kg)-treated rats. Left arrow signals VEH/FPPQ administration, right arrow signals phencyclidine (PCP) administration. The figure includes Neutral-Red stained coronal sections of the rat brain at the level of the site of recording (Paxinos and Watson, 2005). Abbreviations: b, beta; d, delta; g, gamma; HFO, high-frequency oscillations; t, theta. Data are expressed as percentage of basal values (mean ± SEM). Two-way ANOVAs with treatment (T) and time (t) as factors were: (A) d: T (F(1,8) = 1.20; ns), t (F(19,152) = 1.68; P < .05), Tt (F(19,152) = 0.50; ns); t: T (F(1,9) = 9.94; P < .05), tt (F(19,171) = 1.68; P < .05), Ttt (F(19,171) = 0.50; ns); b: T (F(1,9) = 3.09; ns), t (F(19,171) = 4.02; P < .01), Tt (F(19,171) = 1.72; P < .05), tt (F(19,171) = 18.30; P < .01), Ttt (F(19,171) = 49.06; P < .001), TTTt (F(19,171) = 10.45; P < .001), HFO: T (F(1,9) = 13.72; P < .01), t (F(19,171) = 6.58; P < .001). (B) d: T (F(1,8) = 0.51; ns), t (F(19,152) = 1.76; P < .05), Tt (F(19,152) = 0.50; ns); t: T (F(1,9) = 7.13; P < .05), tt (F(19,171) = 10.22; P < .001), Ttt (F(19,171) = 2.26; P < .05), TTt (F(19,171) = 4.24; P < .01), TTTt (F(19,171) = 2.53; P < .01), TTTTt (F(19,171) = 0.77; P < .05), TTTTTt (F(19,171) = 1.24; P < .01); b: T (F(1,9) = 6.77; P < .05), t (F(19,171) = 7.13; P < .05), Tt (F(19,171) = 4.24; P < .01); g: T (F(1,9) = 2.26; ns), t (F(19,171) = 4.24; P < .01), Tt (F(19,171) = 2.53; P < .01), Tt (F(19,171) = 0.50; ns), Ttt (F(19,171) = 0.50; ns), TTTt (F(19,171) = 4.24; P < .01), TTTTt (F(19,171) = 2.53; P < .01), TTTTTt (F(19,171) = 0.50; ns), TTTTTTt (F(19,171) = 0.50; ns).
In summary, and notwithstanding the limitation of using only male rats, the present observations indicate that FPPQ re-
cogent effects of FPPQ as a potential candidate for the treatment of schizophrenia.

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Interest Statement

P.C. was PI of a grant agreement between IDIBAPS and Spherium. During the last 2 years, F.A. has received educational honor-
aria from Lundbeck and was PI of a grant agreement between IDIBAPS and Lundbeck. L.R.-A. and M.C. were employees of Spherium at the time the experiments were performed. The rest of authors declare no conflict of interest.

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