

Potential of the metabotropic glutamate receptor subtype 5 modulates dopaminergic neurotransmission

Nellie Byun^{1,2}, Ayan Ghoshal^{1,3}, Nathaniel D. Kelm^{2,4}, Robert L. Barry^{2,5}, Wellington Pham^{2,5}, Carrie K. Jones^{1,3}, John C. Gore^{2,5}, and P. Jeffrey Conn^{1,3}

¹Vanderbilt Center for Neuroscience Drug Discovery, Nashville, TN, United States, ²Vanderbilt University Institute of Imaging Science, Nashville, TN, United States,

³Pharmacology, Vanderbilt University Medical Center, Nashville, TN, United States, ⁴Biomedical Engineering, Vanderbilt University, Nashville, TN, United States,

⁵Radiology & Radiological Sciences, Vanderbilt University Medical Center, Nashville, TN, United States

Introduction

Previous preclinical studies have demonstrated the potential of compounds that target the metabotropic glutamate receptor subtype 5 (mGluR5) for the treatment of schizophrenia. Both typical and atypical antipsychotic drugs suppress amphetamine (Amph)-induced hyperlocomotion in rodents, so this model is considered to be able to predict the antipsychotic efficacy of a compound. Older generations of mGluR5 positive allosteric modulators, represented by CDPBP and ADX47273, have shown efficacy in this model [1,2]. VU0360172 (N-cyclobutyl-6-((3-fluorophenyl)ethynyl)nicotinamide hydrochloride) is an optimized, selective mGluR5 PAM with both i.p. and oral availability, which reverses Amph-induced hyperlocomotion in rats [3]. Here we used VU0360172 and pharmacologic MRI (phMRI) to determine whether potentiation of mGluR5 could attenuate Amph-induced brain activation and to assess the specific brain regions underlying the compound's ability to modulate Amph-induced cerebral blood volume (CBV) changes.

Methods

Protocol: Adult male Sprague-Dawley rats were intubated and mechanically ventilated under neuromuscular blockade (pancuronium bromide 1 mg/kg, i.p.). Isoflurane (0.88%) was delivered in a gas mixture of O₂:N₂O (1:2). Heart rate, respiration rate, temperature, and end-tidal CO₂ were continuously monitored. The following groups were scanned: Veh/Veh, Veh/Amph, and VU0360172/Amph. In a separate set of studies, VU0360172 (30 mg/kg, i.p.) or vehicle (Veh) was used as the drug challenge. **phMRI:** We acquired functional images on a Varian 9.4T Varian scanner with a Doty Litz 38 coil. Structural and functional images were acquired with a T2-weighted fast spin echo (fse) sequence (11, 1.5mm thick slices). High resolution fse anatomical images were collected (TR = 2550 ms, TE_{eff} = 40 ms, acquisitions = 2, matrix = 256 × 256) to facilitate registration. After acquiring 7 initial images (TR = 2500 ms, TE_{eff} = 36 ms, acquisitions = 2, matrix = 64 × 64, one image every 41.6 s) to determine the pre-contrast baseline, superparamagnetic iron oxide (SPIO) nanoparticles (20 mg/kg, i.v.) were injected. VU0360172 (30 mg/kg i.p.) or Veh was then administered. The post-SPIO functional scan consisted of a 15 min baseline, followed by Amph (1 mg/kg, i.p.) or Veh 30 min after VU0360172 injection, then images were acquired for another 45 min. **Data analysis:** Following within-subject registration, images from each subject were co-registered with a template rat using AFNI. Fractional CBV change, ΔCBV/CBV₀, was calculated as $[\ln(S(t)/S_0)]/[\ln(S_0/S_{pre})]$, where S₀ is the average baseline signal and S_{pre} is the average pre-MION signal [4] and fractional CBV time courses were extracted from regions of interest (ROIs).

Results

The selective mGluR5 PAM VU0360172 alone increased CBV in a global manner with similar sustained patterns in all the ROIs analyzed. In the VU0360172-Amph drug interaction studies, acute administration of Amph (Veh/Amph group) produced robust, sustained CBV increases in cortical, thalamic, and striatal regions in anesthetized rats. Despite the underlying CBV contribution from VU0360172, pretreatment with VU0360172 suppressed the amplitude of the CBV response to Amph in the prefrontal cortex with trends toward decrease in the cingulate, and retrosplenial cortices (Fig. 1). Suppression of the Amph response was not observed in striatum.

Discussion

The phMRI results show the underlying action of VU0360172 in the brain. We hypothesize that the global CBV increases induced by VU0360172 alone is due to increased neurovascular coupling via astrocytic mGluR5. In the reversal of Amph brain activation studies, the CBV responses produced by VU0360172 itself could be masking any action in the striatum, but despite this, suppression of the Amph response were detectable in cortical areas. These data, along with behavioral findings, are helping to validate the potential utility of mGluR5 potentiators for the treatment of schizophrenia and the multiple roles of mGluR5 in the brain.

References

1. Kinney GG et al., JPET. 306:116-123 (2003).
2. Liu F et al., JPET. 327:827-839 (2008).
3. Rodriguez AL, et al., Mol Pharmacol. 78:1105-23 (2010).
4. Mandeville JB et al., Magn Reson Med. 39: 615 (1998).

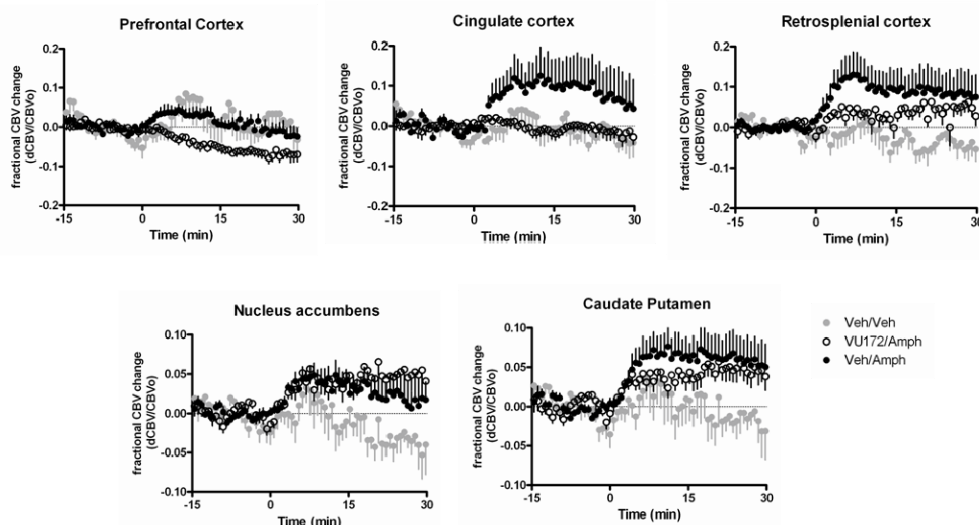


Fig. 1: VU0360172 pretreatment suppressed the amphetamine response (VU172/Amph n=8 vs Veh/Amph n=8) in prefrontal cortex, with trends in cingulate and retrosplenial cortices. No reversals were observed in the striatum (nucleus accumbens, caudate putamen).