Potentiation of the metabotropic glutamate receptor subtype 2 blocks phencyclidine-induced brain activation: a phMRI study

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Introduction

Previous preclinical and clinical studies have demonstrated the therapeutic potential of compounds that directly activate metabotropic glutamate receptor subtypes 2 and 3 (mGluR2/3) for the treatment of schizophrenia. Here we utilized a selective mGluR2 compound, biphenyl indanone-A (BINA), an allosteric potentiator, for pharmacologic MRI (phMRI) since BINA has been shown to be effective in mouse behavioral models of psychosis[1]. In this study, we utilized the PCP rat model predictive of schizophrenia to determine whether potentiation of mGluR2 could attenuate PCP-induced brain activation and to assess the specific brain regions underlying BINA's ability to modulate PCP-induced functional changes.

Methods

phMRI: We acquired functional images on a Varian 7T scanner using a gradient echo sequence (TR=200 ms, TE=12 ms, α=20°, NEX=2, 64×64×8 matrix, 30×30×2 mm FOV). High resolution fast spin-echo structural MR images were also collected (TR=4000 ms, echo spacing=10 ms, average=2, matrix=256 × 128, thickness=2 mm) to facilitate registration. Protocol: Adult male Sprague-Dawley rats were tracheotomized and mechanically ventilated under 0.8% isoflurane delivered in a gas mixture of 33:67% O_2/N_2O. Heart rate, respiration rate, temperature, and end-tidal CO_2 were continuously monitored. Following a 20 min baseline period, pretreatment drug, BINA (32 mg/kg, i.p.) or vehicle (Veh), was administered. After 30 min, challenge drug PCP (5.6 mg/kg, i.p.) or vehicle (Veh) was injected, so that the following groups were scanned (N=5-7 each): Veh/Veh, Veh/PCP, BINA/PCP, BINA/Veh. Data analysis: For each subject, raw image intensities were converted to percent BOLD signal change relative to the pre-challenge baseline period ($\Delta S/S_0$) using principal component analysis. Time series data were temporally smoothed by applying a 3-point Hamming window and linearly detrended to correct for baseline signal drift (MATLAB). For group statistical analyses, area under the curve (AUC) were compared using one-way ANOVA and Dunnett's *post hoc* tests ($p<0.05$ significant). Group AUC maps were generated using AFNI. Processed images for each treatment condition were group-averaged and co-registered to anatomic reference images. Behavior: For the locomotor experiments, the same dose groups as in the phMRI studies (N=8-12 each) were tested were in open field chambers equipped with photobeams. After 30 min in the chamber, the animal was pretreated with BINA or Veh, returned to the chamber for another 30 min, then injected with PCP or Sal, followed by locomotor measurements for 60 min. The total number of beam breaks in the final 60 min was statistically compared.

Results

Acute administration of PCP produced robust, sustained BOLD activation in cortical, thalamic, and striatal regions in the anesthetized rat (Fig. 1). Pretreatment with BINA suppressed the amplitude of the BOLD response to PCP in the prefrontal cortex, caudaute-putamen, and mediodorsal thalamus (Fig. 1), which corresponds to areas that express mGluR2. BINA was also effective at the behavioral level, significantly decreasing PCP locomotor acitivity.

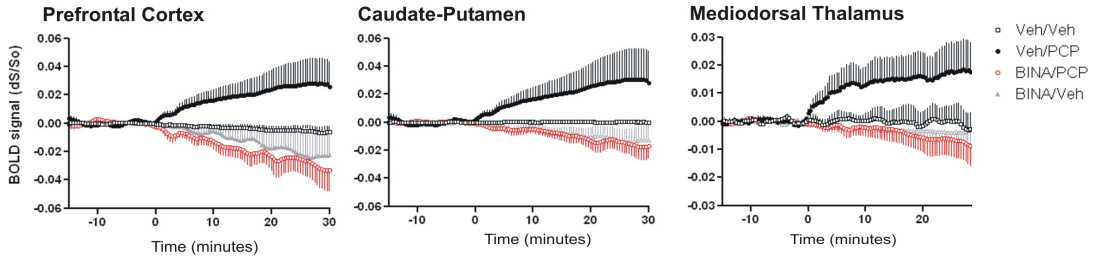

Fig. 1. Time course of BOLD response in specific brain regions. BINA pretreatment suppresses PCP-induced brain activation in the prefrontal cortex, caudate putamen, and mediodorsal thalamus.

Conclusions

Our results show key brain structures underlying the pharmacological action of BINA in reversal of PCP-induced hyperexcitation in a preclinical model of schizophrenia. The phMRI and behavior data demonstrate that potentiation of mGluR2 can decrease brain excitation. The phMRI and behavioral findings bolster the growing body of evidence that mGluR2 is a viable target for the treatment of schizophrenia.

Ref. 1. Galici, R, Jones, CK, et al. 2006. J Pharmacol Exp Ther. 318, 173-185.