Pre-pubertal clozapine administration prevents post-pubertal emergence of brain structural pathology in an animal model of schizophrenia

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Introduction

Schizophrenia is a severe neuropsychiatric disorder whose clinical course is characterized by the onset of symptoms after puberty and whose pharmacotherapy remains unsatisfactory. While much evidence indicates that schizophrenia is associated with a brain insult early in development, there is increasing evidence from longitudinal magnetic resonance imaging (MRI) studies, that progressive structural brain aberrations occur in this disorder, and indeed precede the onset of symptoms, intensifying prior to transition to psychosis (1). These data have raised a crucial question of whether schizophrenia can be prevented. Studies in individuals in the early clinical stages of the disorder yet prior to the development of the full clinical phenotype have been encouraging in showing that preventive treatment with atypical antipsychotic drugs (APDs) may reduce the risk of progression to first-episode psychosis in some of the patients but controversies remain. To date, it is still unknown whether progressive structural brain aberrations can be halted by preventive treatments. Using animal models of schizophrenia can considerably aid in evaluating the feasibility of prevention. Of particular relevance are the neurodevelopmental models which mimic the clinical course of this disorder, in which the deleterious functional consequences of early insult do not arise until after puberty. We used the maternal immune activation a model of schizophrenia to assess the efficacy of the atypical antipsychotic clozapine to prevent neuroanatomical deterioration.

Materials and methods

Pregnant rats injected on gestational day 15 with the viral mimic- PolyI:C or saline. During adolescence (days 34–47) period, male offspring of Poly I:C-and saline-treated dams received daily clozapine (7.5mg/kg) or saline injection. Behavioral testing and imaging were performed at adulthood (from 90 days). MRI studies were performed using the 7T scanner (Bruker). The protocol included quantitative T_2 mapping [T_2 map obtained using spin echo, TR = 3000 ms and 16 echo times (10-160 ms), matrix dimension of 256x 28 (reconstructed to 256x256), with final pixel size of 0.117x0.117mm^2, 12 slices of 1.5-mm thick], and DTI that was obtained using a diffusion-weighted (DW) spin-echo, echo-planar-imaging (EPI) pulse sequence with the following parameters: TR/TE = 4000/25ms, Δ/δ=10/4.5ms, 4 EPI segments and 15 non-collinear gradient directions with a single b value = 1000 sec/mm^2 and one image with b value of 0 sec/mm^2 (b0) , 16 slices of 1.5 mm thickness and in-plane resolution of 0.234x0.312mm^2. Image Analysis: T_2 map were extracted from the multi-echo signal that was fitted to a mono-exponential decay function on a pixel-by-pixel basis. The DTI analysis was done using an in-house software to calculate the different DTI indexed maps (FA (fractional anisotropy), ADC (apparent Diffusion Coefficient), radial, and axial diffusivities (λ1 , λ2 , λ3). For statistical analysis, each rat brain was normalized to the template images included: bias correction, co-registered with the template, normalization and smoothing. All image transformations and statistical analyses were carried out using SPM2. T_2 maps were also used for volumetric calculation of hippocampus (HP), striatum (STR), prefrontal cortex (PFC) and lateral ventricle (LV).

Results

Prenatal Poly I:C treatment induces a decrease in HP, STR and PFC volume with enlargement of LV. Clozapine pre-treatment prevents LV enlargement and smaller HP but failed to prevent the decrease in STR and PFC volume (Figure 1).
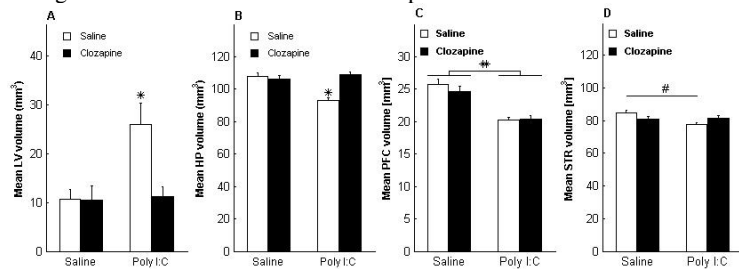

Figure 1. Prenatal Poly I:C and Clozapine treatment affect LV (A), HP (B), PFC(C) and STR (D) volume. Mean±SEM T_2 volumes (n=7–12). * Significant difference between offspring of Poly I:C dams and the other 3 groups, **Significant difference between offspring of Poly I:C dams and offspring of saline dams, # Significant difference between offspring of Poly I:C dams treated with saline and offspring of saline dams treated with saline (p values<.005).

The same pattern was found using the quantitative T_2 map method. Poly I:C induced an increase in T_2 values in HP, STR and PFC. Clozapine prevented this increase in HP (Figure 2A) but failed to prevent it in STR and PFC (Figure 2B). T_2 maps showed an increase in T_2 values also in the thalamus of Poly I:C offspring prevented by clozapin (Figure 2A). This was paralleled by prevention of behavioral abnormalities phenotypic of schizophrenia, attentional deficit and hypersensitivity to amphetamine.
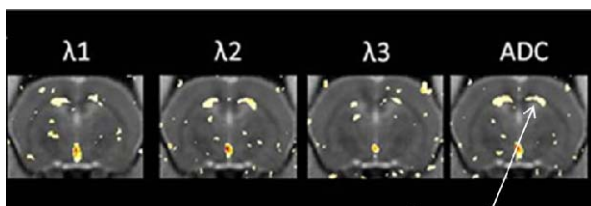

Figure. 3. Clozapine prevents the increase in ADC, λ₁ , λ₂ , λ₃ values in the corpus callosum. Figure 3 presents the prenatal x preventive interaction of the fore calculated maps (ADC, λ₁ , λ₂ , λ₃) showing the preventive effect of clozapine treatment as revealed by significant interactions and post hoc analyses (p<0.05).
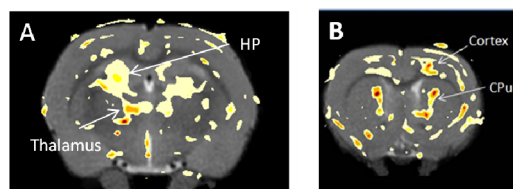

Figure 2. Prenatal Poly I:C and Clozapine treatment affect T_2 values. Figure 2A presents the prenatal x preventive interaction; changes in HP and Thalamus found to be prevented by clozapine treatment as revealed by the presence of significant interactions and post hoc analyses. Figure 2B presents the main effect of prenatal treatment; poly I:C increased the T_2 values in STR and PFC and Clozapine failed to prevent those changes.

Conclusion

This is the first demonstration that pharmacological intervention during adolescence can prevent the emergence of behavioral abnormalities and same of the brain structural changes resulting from in-utero insult.

References: 1. Lawrie SM, McIntosh AM, Hall J, Owens DG, Johnstone EC (2008): Brain structure and function changes during the development of schizophrenia: the evidence from studies of subjects at increased genetic risk. Schizophr Bull 34:330-340.