Medical Hypotheses 85 (2015) 367–370

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Early antipsychotic intervention and schizophrenia

Yu-Yin Yang [a], Chao-Lin Lu [b], Shih-Mao Lo [b], Chia-Ho Peng [b], Yia-Ping Liu [c,d,*]

[a] Nutrition Unit, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[b] Department of Psychiatry, Beitou Branch, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC
[c] Department of Physiology and Biophysics, National Defense Medical Center, Taipei, Taiwan
[d] Department of Psychiatry, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, ROC

ARTICLE INFO

Article history:
Received 20 January 2015
Accepted 18 May 2015

ABSTRACT

Schizophrenia is a major mental disorder in which patients' cognitive functions gradually deteriorate. Pharmacological intervention with antipsychotics has proven effective, yet it is still debatable whether to initiate treatment in patients' premorbid stage. Based on the developmental origins of schizophrenia, we hypothesize that for those who are at high risk for schizophrenia, particularly with gating problems, an early pharmacological intervention would be beneficial. We performed a pilot rodent study to evaluate this hypothesis. Our results demonstrated that isolation rearing-induced sensorimotor gating dysfunction could be reversed by a chronic risperidone regimen initiated at different age time points. As expected, interventions that we initiated earlier (in adolescent stage) appeared to have better efficacy than interventions initiated four weeks later (in young adult stage). Our hypothesis may contribute new insight for both prevention and treatment of schizophrenia.

Introduction

Schizophrenia is a major mental disorder in which patients suffer from multidimensional malfunctions in a deteriorating manner [1]. Pharmacological intervention with antipsychotics has been proven effective in managing the symptoms of schizophrenic patients, thus resulting in a better prognosis [2]. However, whether an earlier intervention is necessary remains unknown. Not taking antipsychotics in the prodromal phase of schizophrenia mainly comes from the fact that (i) symptoms are not full-blown in the prodromal stage and some adolescents with prodromal signs did not show any sign of psychiatric illness later (i.e., false-positive) [3,4], (ii) there is a potential risk of stigmatizing patients as psychotic and doomed to chronic illness [5,6], and (iii) drugs may cause long-term side effects with possible morphological changes in the brain [7,8]. This evidence results in an ethical dilemma regarding early antipsychotic intervention [9]. Thus, early antipsychotic intervention is a topic involving ethics, neuroscience, preventive medicine, and health policy.

However, the introduction of second-generation antipsychotics (SGAs) that were developed in the mid-1990s led to a paradigm shift in early intervention ethics; SGAs were proven to have equal efficacy in comparison with traditional neuroleptics with fewer side-effects [5], and SGAs were used to prevent the relapse of the symptoms [9]. The rationale is based on considering schizophrenia to be a developmental disorder. Thus, the biological method should help impede the progress of the disorder and prevent the patients from receiving too much biochemical disturbance before they are aware of the symptoms.

Developmental theory suggests that the evolution of schizophrenia follows a dynamic process. This process starts early in patients' lives, and as time goes by, symptoms become full-blown around patients' puberty stages. Their performance, including cognitive functions in particular, is gradually disabled in an irreversible manner thereafter [10]. Developmental theory maintains that the growth of an individual comprises several stages in a scheduled order, in which each stage must be satisfactorily resolved [11]. Based on this conceptual framework, perceptual symptoms such as auditory and visual hallucinations, among other cardinal characteristics of schizophrenia, may be related to certain developmental deviations with a pathological origin. This is particularly relevant in terms of sensory gating dysfunction, as it fails to filter out unimportant or unnecessary stimuli from the environment [12]. This failure is hypothetically considered to be relevant to the pathogenesis of hallucination [13]. However, neurodevelopmental evidence also reveals that negative symptoms in patients' premorbid stages or first psychotic episodes respond poorly to antipsychotics [14]. Pre-attentional gating dysfunction

* Corresponding author at: Department of Physiology and Biophysics, Department of Psychiatry, National Defense Medical Center, 161 Minchuan East Rd., Sec. 6, Taipei 114, Taiwan, ROC. Tel.: +886 2 87923100x18614.
E-mail address: yiaping@ndmctsgh.edu.tw (Y.-P. Liu).

http://dx.doi.org/10.1016/j.mehy.2015.05.014
0306-9877/

would be potentially useful in defining the appropriate target population for early antipsychotic intervention.

Hypothesis

The hypothesis described here is an extension of what is mentioned above, with a potentially pragmatic rationale in terms of how to reverse or alleviate the gating dysfunction-related endophenotype of schizophrenia. We hypothesize that early antipsychotic intervention, particularly before the emergence of full-blown schizophrenic symptoms (i.e., at premorbid stage), would be particularly beneficial in patients with sensory gating problems.

Evaluation of the hypothesis

Establishment of rodent model of schizophrenia with gating dysfunction characteristics

We employed a schizophrenia rodent model to evaluate our hypothesis. The model is based on developmental theory and is known to cause a gating problem. Rats reared in social isolation from weaning (isolation rearing, IR) are acknowledged to model schizophrenia-spectrum disorders; they show impairments in recognizing novel objects [15,16], attentional set-shifting [17,18], and gating pre-attentional sensorimotor stimulus ability [19]. IR rats are hyperactive in their central dopaminergic system, which is the common mechanism shared by sensorimotor gating deficit and schizophrenia [20]. However, the interpretation of schizophrenia based on IR effects should be noted because some of these effects are strain and sex-dependent [21,22].

IR rats are particularly suitable to be employed in the developmental theory of schizophrenia because these rats have been socially isolated from their early life. Increasing evidence has demonstrated that this sensorimotor gating deficit is unable to be reversed by re-socialization; therefore, a time window or so-called critical period for the normal gating ability to develop exists [23,24]. Accordingly, if our hypothesis is correct, earlier pharmacological intervention should be more beneficial in recovering IR-induced sensorimotor gating impairment.

Methods and study design

Twenty-eight IR rats (weaned at postnatal day 21) in adolescence (postnatal seven weeks) or young adulthood stages (postnatal 11 weeks) were randomly assigned to a saline or risperidone regimen (1 mg/kg/day, for four weeks, for each group, $N = 4$, see Fig. 1). Eight social control rats were employed to contrast the

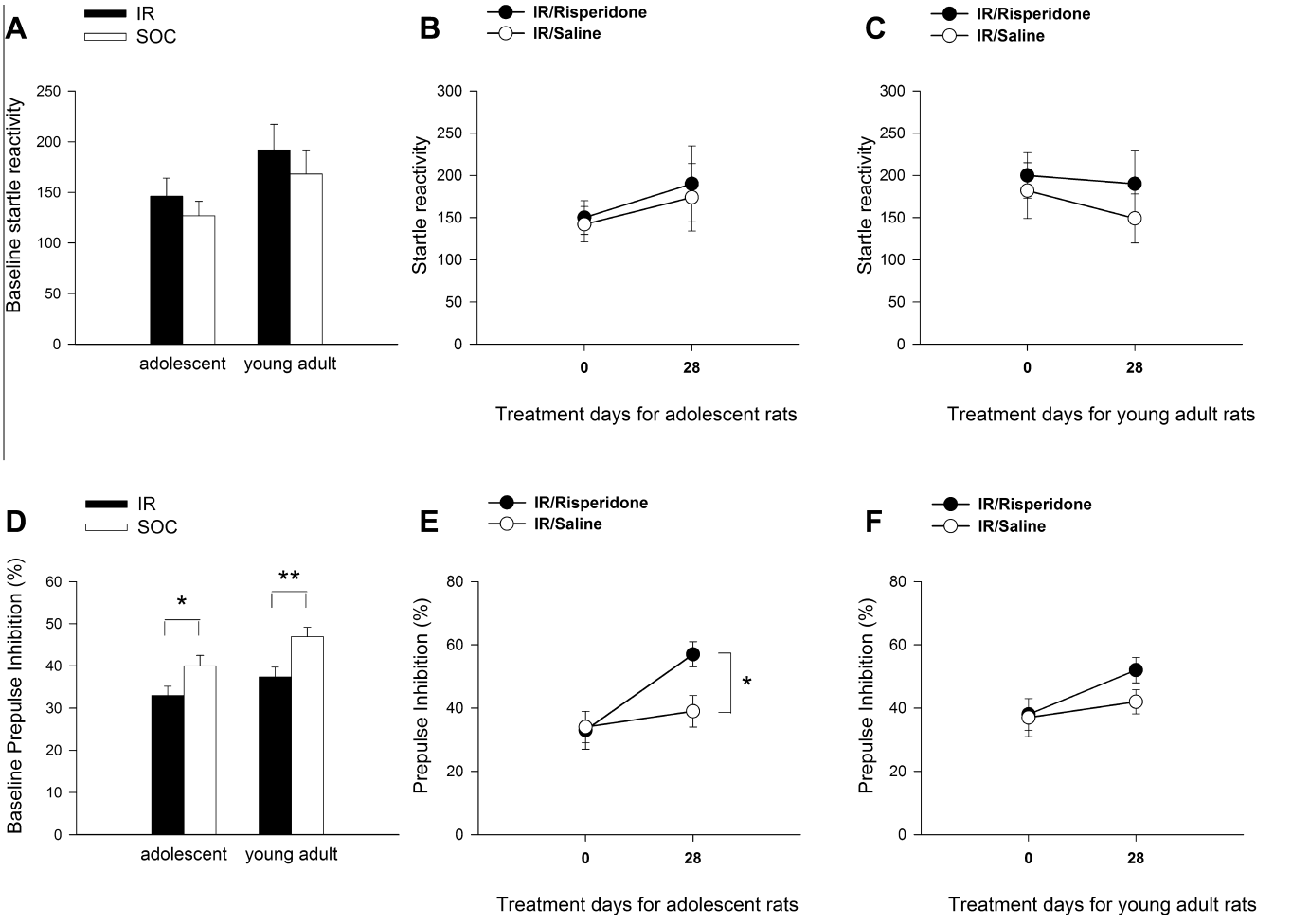

Fig. 1. There is no significant effect on startle reactivity (arbitrary units) between isolation rearing (IR) and social control (SOC) rats (A) or between saline or risperidone adolescent (B) or young adult (C) IR rats. Isolation reared (IR) rats have an inferior prepulse inhibition ability in comparison with their social controls (SOC) (D). Early intervention is beneficial in IR-induced sensorimotor gating deficit (adolescent IR/Risperidone, adolescent IR/Saline, young adult IR/Risperidone, and young adult IR/Saline, for each group, $N = 4$) because risperidone is more effective in adolescent (E) rats in comparison with young adult IR rats (F), and the risperidone-increased PPI in adolescent IR rats is higher than that of young adult IR rats. Data are represented as group averages ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$.