GLUTATHIONE DEFICIT DURING BRAIN DEVELOPMENT INDUCES SCHIZOPHRENIA-LIKE SYMPTOMS IN THE ADULT SPRAGUE-DAWLEY RATS

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INTRODUCTION

Schizophrenia is a chronic, most devastating psychiatric illness affecting about 1% of the world population. It develops progressively, remaining often undetected during childhood and adolescence, with the first episodes of psychosis that appear at early adulthood. Although symptoms of schizophrenia are well characterized, a clear mechanism underlying the pathogenesis of the disease still remains unknown. Recently, it has been demonstrated in few clinical reports that glutathione (GSH) levels are reduced in the medial prefrontal cortex and striatum of schizophrenic patients [1,2,3]. The consequences of brain GSH deficit during development were studied in the above-mentioned animal models in adulthood. Those studies demonstrated that chronic combined treatment of Osteogenic Disorder Shionogi (ODS) mutant rats, which, like humans, cannot synthesize ascorbic acid, with the inhibitor of glutathione (GSH) synthesis L-buthionine-(S,R)-sulfoximine (BSO) and the inhibitor of dopamine (DA) reuptake GBR 12909 during early postnatal life induced schizophrenia-like memory deficits during adulthood [4]. These data suggest that schizophrenia is associated with an important brain glutathione deficit.

AIM

In the present study we used animal model, defined as the neurodevelopmental model of schizophrenia, in which the schizophrenia-like changes we induced by chronic administration the inhibitor of glutathione (GSH) synthesis L-buthionine-(S,R)-sulfoximine (BSO) and the inhibitor of dopamine (DA) reuptake GBR 12909, alone or in combination to male Sprague-Dawley pups between the 5th and 16th day of postnatal life (period of intense synaptogenesis). In this model, changes in the rats' behavior were evaluated in the adult rats.

MATERIALS AND METHODS

Between postnatal day p5 and p16, pups (Sprague-Dawley, male) were treated subcutaneously with the inhibitor of glutathione synthesis, BSO (3.8 mmol/kg, sc, daily) or the dopamine uptake inhibitor, GBR 12909 (5 mg/kg, sc, on even days), and also BSO together with GBR 12909 or vehicle [4]. On p21 rats was weaned and housed in groups of four to five until p92. On p30-32, p42-43, p60-61 and p90-92 rats were tested in the social interaction and novel object recognition or prepulse inhibition (PPI) tests.

Social interaction test in rats

The social interaction test was performed using a PCV box (67 cm × 57 cm × 30 cm, length × width × height). The arena was dimly illuminated with an indirect light of 18 Lux [5]. Each social interaction experiment involving two rats was carried out during the light phase of the light/dark cycle. The rats were selected from separate housing cages to make a pair for the study. The behavior of the animals was measured over a 10-min period. Social interaction between two rats was expressed as the total time spent in social behavior, like such as sniffing, genital investigation, chasing and fighting with each other. The number of episodes was counted as a separate paradigm. Each group composed of 12 rats (6 pairs).

The novel object recognition test in rats

The novel object recognition (NOR) test was performed using a black PCV box (67 cm × 57 cm × 30 cm, length × width × height). The arena was dimly illuminated with an indirect light of 18 Lux. On the first day of the experiment (adaptation), rats was placed in the box for 10 minutes. On the next day (T1), the animals was placed in the box for 5 minutes with two identical objects (white tin, 5 cm wide and 14 cm high or green pyramid 5 cm wide and 14 cm high). The time of objects interest will be measured in each of the two objects separately. Then, one hour after T1, the rats again will be placed on the box for 5 min (T2), with two different objects one of the previous session (old) and the other new (white box and green pyramid). The time of objects interest will be measured in each of the two objects separately (sniffing, touching or climbing). Each group composed of 8 rats.

RESULTS

Social interaction test

Novel object recognition test

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ vs. veh, # $P < 0.05$, ## $P < 0.01$, ### $P < 0.001$ vs. BSO, $\Delta P < 0.05$, $\Delta\Delta P < 0.01$, $\Delta\Delta\Delta P < 0.001$ vs. GBR

Prepulse inhibition test

SUMMARY AND CONCLUSION

- The obtained results showed that BSO (3.8 mmol/kg, daily), alone or in combination with GBR 12909 (5 mg/kg, on even days) induced deficits in adult rats (p42, p60 and p90) in the social interaction test.
- BSO (3.8 mmol/kg, daily), alone or in combination with GBR 12909 (5 mg/kg, on even days) induced deficits in memory retention in adult rats (p43, p61 and p91) in the novel object recognition test and reduced the prepulse inhibition (PPI) on p92.
- The present study suggests that the inhibition of glutathione synthesis in early postnatal development rats induces long-term deficits in the behavioral tests in adult rats. These symptoms are also observed in schizophrenic patients.

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