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Olig2 Silence Ameliorates Cuprizone-Induced Schizophrenia-Like Symptoms in Mice

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

A 1 Hongxia Liu
BCDE 2 Jinguo Zhai
C 1 Bin Wang
BC 3 Maosheng Fang

1 Jining Neuro-Psychiatric Hospital, Jining, Shandong, P.R. China
2 Jining Medical University, Jining, Shandong, P.R. China
3 Wuhan Mental Health Center, Wuhan, Hubei, P.R. China

Corresponding Author: Jinguo Zhai, e-mail: zhaijinguo2015@163.com
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Background: The pathogenesis of schizophrenia is complex and oligodendrocyte abnormality is an important component of the pathogenesis found in schizophrenia. This study was designed to evaluate the function of olig2 in cuprizone-induced schizophrenia-like symptoms in a mouse model, and to assess the related mechanisms.

Material/Methods: The schizophrenia-like symptoms were modeled by administration of cuprizone in mice. Open-field and elevated-plus maze tests were applied to detect behavioral changes. Adenovirus encoding olig2 siRNA was designed to silence olig2 expression. Real-time PCR and western blotting were applied to detect myelin basic protein (MBP), 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), glial fibrillary acidic protein (GFAP) and olig2 expressions.

Results: Open field test showed that the distance and time spent in the center area were significantly decreased in cuprizone mice (model mice) when compared with control mice ($p<0.05$). By contrast, olig2 silence could significantly increase the time and distance spent in the center area compared with the model mice ($p<0.05$). As revealed by elevated-plus maze test, the mice in the model group preferred the open arm and spent more time and distance in the open arm compared with control mice ($p<0.05$), while olig2 silence significantly reversed the abnormalities ($p<0.05$). Mechanically, MBP and CNPase expression were reduced in the model group compared with the control ($p<0.05$). However, olig2 silence reversed the reduction caused by cuprizone modeling ($p<0.05$). In addition, GFAP was elevated after cuprizone modeling compared with control ($p<0.05$), and was significantly inhibited by olig2 silence compared with model ($p<0.05$).

Conclusions: Cuprizone-induced schizophrenia-like symptoms involved olig2 upregulation. The silence of olig2 could prevent changes, likely through regulating MBP, CNPase, and GFAP expressions.

MeSH Keywords: Glial Fibrillary Acidic Protein • Oligodendroglia • Schizophrenia

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Background

Schizophrenia is a common mental illness caused by unconfirmed pathological reasons, often accompanying by behavioral and emotional obstacles [1]. The pathogenesis of schizophrenia is complex; genetics, environmental factors, and social pressure could contribute to disease development and progression. Brain anatomy reveals enlarged ventricular and decreased cortical volume in schizophrenia patients [2,3]. Other evidence has shown that schizophrenia is featured by pathological changes of cerebral white matter [4–8]. The alteration of white matter prohibits the communication between regions and causes schizophrenia-like symptoms.

Cuprizone (CPZ) is a copper chelating agent and has toxic action in the central nervous system [9]. CPZ injection leads to demyelinating lesions, while myelin sheath will regenerate after stopping the use of CPZ. Therefore, CPZ is widely applied to model physiological changes in the process of remyelination [10,11]. The symptoms observed in this model are similar to those observed in schizophrenia patients. Interestingly, it has been reported that quetiapine could ameliorate schizophrenia-like behaviors and protect myelin integrity in cuprizone intoxicated mice [12]. Therefore, the CPZ model is also used to investigate the changes of corpus callosum in schizophrenia [11].

Oligodendrocyte gene (olig) transcription factor family was first proposed by Takebayashi et al. in 2000 [13] and is comprised of olig1, olig2, and olig3. The olig2 gene is located on chromosome 21 in humans and chromosome 16 in rats. Olig2 encodes basic helix-loop-helix transcription factors and is preferentially expressed in the progenitor cells, and regulates the differentiation of progenitor cells into neurons or glial cells [14]. Embryonic stem cells derived glial progenitor cells can differentiate into oligodendrocyte precursor cells upon *in vitro* induction, promoted by olig2 overexpression [15]. Oligodendrocyte abnormality is an important component of the pathogenesis found in schizophrenia. However, most studies have focused on the single nucleotide polymorphisms of olig2 in schizophrenia [16]; and expression change of olig2 in schizophrenia has not been confirmed [17,18].

This study aimed to explore the expression of olig2 in a CPZ mice model and the role of olig2 in cuprizone-induced schizophrenia-like symptoms. We found that olig2 was promoted in CPZ mice and silencing olig2 expression could ameliorate schizophrenia-like symptoms.

Material and Methods

Animals and groups

A total of 40 male C57BL/6 mice (25 g, 4-month old) were obtained from Hunan SJA Experimental Animal Company (Hunan, China). The animal use and experimental protocol were under the approval of Ethics Committee of Jining Neuro-Psychiatric Hospital. The mice were randomly divided into four groups (n=10 in each group): control group (NC), CPZ model group (CPZ), CPZ+olig2 NC group, and CPZ+olig2-siRNA group. Olig2 siRNA was encoded in adenovirus olig2 (Rochen Pharma Co., Ltd., Shanghai, China). The adenovirus without olig2 siRNA served as the control. Mice in the CPZ model group were fed with a diet containing 0.2% (w/w) CPZ powder for six weeks, while mice in the control group were fed with a normal diet. At the end of fourth week, the mice in CPZ+olig2 NC group and CPZ+olig2-siRNA group were injected intravenously with 0.2 mL adenovirus. After other two-week feeding with CPZ, behavioral tests were conducted and the prefrontal cortex was collected for real-time PCR and biochemical experiments.

Open-field test (OPT)

The open-field test was conducted in a plastic box (25×25×25 cm). Before each test, the equipment was confirmed to be clean and taste-free. The animal was placed in the center of the "field" and time was started immediately and continued for a five-minute interval; the behavior was recorded by video capture software for five minutes. The total distance and time in the center area were measured.

Elevated-plus maze (EPM)

Mice were put in the center of the equipment with their head facing the open arm. The animal activity was recorded for five minutes. After the experiments, the mice were returned to their cages. The time and distance spent in the open arm were recorded.

Real-time PCR (RT-PCR)

The prefrontal cortex was collected for real-time PCR. Total RNA was extracted according to the instruction of TRIzol kit (Dalian Baosheng, Dalian, China) and the purity of RNA was confirmed by optical density (OD)280/OD260. RNA was amplified by one-step RT-PCR kit (Dalian Baosheng, Dalian, China), and the PCR products were detected by 2% agarose gel electrophoresis according to a protocol previously described [19]. The primers were added into a 25-μL PCR reaction system following a protocol of 94°C denaturation for 45 seconds, 59°C annealing for 45 seconds, 72°C extension for 60 seconds, for 35 cycles. The primers were listed as follows:

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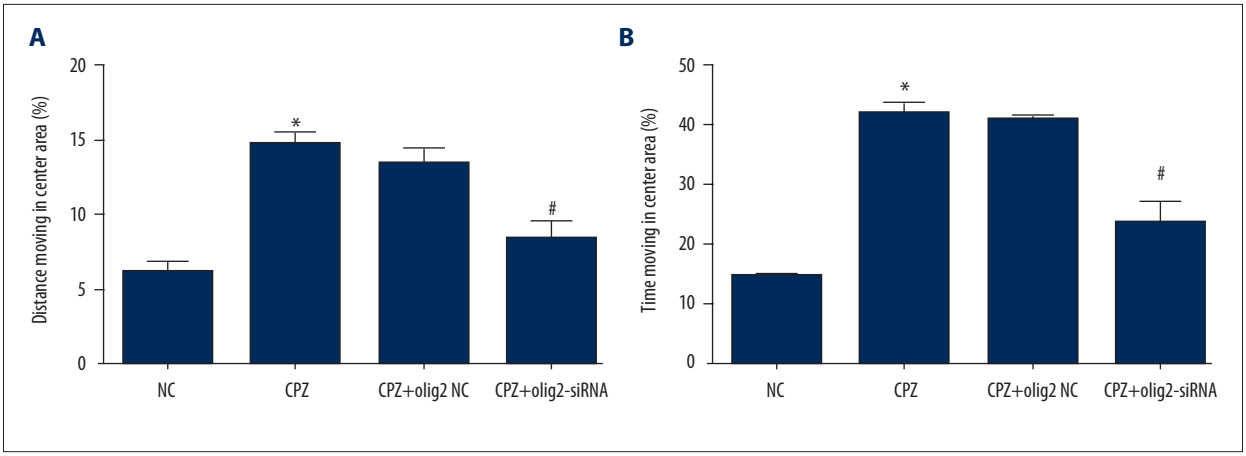

Figure 1. Olig2 silence mitigates cuprizone-induced decrease of distance and time spent in the center area. (**A**) Distance in center area; (**B**) time in center area. * $p<0.05$ compared with control; # $p<0.05$ compared with CPZ+olig2 NC group.

Olig2-F: GTACACGGTCCACCGCCG,
Olig2-R: GCTCCCGCTGAACTCCTCCG;
MBP-F: ACCCACTATGGCTCCCTG,
MBP-R: CAATCCTCTTCCCTTTCCTT;
GFAP-F: AAGACACTGTGGCTCGTC,
GFAP-R: CTTCCTGTAGGTGGCAAT;
CNPase-F: TGGACAAGTACCGTGATGGC,
CNPase-R: TTCCCGTTCGTGGTTGGT;
β-actin-F: CCTGTATGCCTCTGGTCG,
β-actin-R: GGCGTAACCCTCGTAGAT.

Western blotting

The protein was extracted by RIPA cell lysate (containing PMSF) as previously described [20]. Protein samples were heated at 100°C for 10 minutes, and the protein concentration was quantified using BCA protein assay kit (Beyotime Institute of Biotechnology, Shanghai, China). Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) was processed and proteins were later transferred onto nitrocellulose membrane. The membrane was blocked with 5% nonfat milk in PBST at room temperature for two hours. The primary antibodies (MBP, CNPase, GFAP, and olig2 antibodies, 1: 1,000, Abcam; Actin, 1: 500, Zsbio, Beijing, China) were incubated with the membrane overnight at 4°C. After washing three times (10 minutes each time), the secondary antibody was incubated with the membrane for two hours at room temperature. Chemiluminescent substrate detection reagent was applied to assist with the staining. The target band was analyzed by ImageJ software for grayscale analysis.

Statistical analysis

The data were expressed as mean and standard deviation (SD) and analyzed using SPSS 17.0. Statistical significance was assessed by one-way ANOVA. A value of $p<0.05$ was considered statistically significant.

Results

Olig2 silence ameliorates the neurobehavioral changes in cuprizone mice

The animals in all groups had normal conditions for drinking and eating. There were no deaths in any of the groups during experiments. Initially, we detected the neurobehavioral changes in the cuprizone mice. As shown in Figure 1, cuprizone administration significantly decreased the time and distance spent in the center area. By contrast, the effect of cuprizone was significantly eliminated by olig2 silence, but not by NC virus. EPM showed that the mice in the model group spent more time and distance in the open arm compared with the control group (Figure 2). Olig2 silence significantly decreased the time and distance spent in the open arm compared with the model group. After the behavioral tests, the mice were decapitated and brain tissues were collected to detect the gene expression.

Olig2 silence decreases olig2 expression in cuprizone mice

As olig2 silence ameliorated the behavioral changes induced by CPZ, we detected olig2 expression in the prefrontal cortex. Figure 3 shows that cuprizone treatment significantly upregulated olig2 expression compared with the control. By contrast, intravenous injection of olig2 silence virus reversed the cuprizone-induced olig2 expression, while NC virus did not affect olig2 expression. The expression of olig2 in different groups was further confirmed by western blotting.

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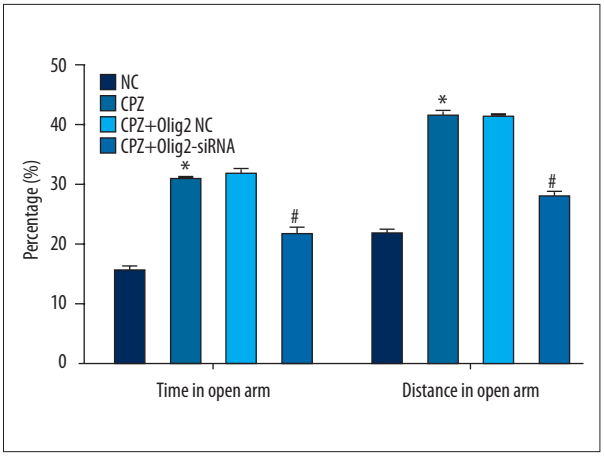

Figure 2. Olig2 silence mitigates cuprizone-induced increase of time spent in the open arm. * $p<0.05$ compared with control; # $p<0.05$ compared with CPZ+olig2 NC group.

Olig2 silence increases MBP and CNPase, but decreases GFAP expression in cuprizone mice

We also detected myelin basic protein (MBP), 2',3'-cyclic nucleotide 3'-phosphodiesterase (CNPase), glial fibrillary acidic protein (GFAP) expressions in the prefrontal cortex. As shown in Figure 4, cuprizone treatment decreased MBP and CNPase expressions, an effect that was reversed by olig2 silence. By contrast, cuprizone treatment increased GFAP expression, an effect that was reversed by olig2 silence. As the control, NC virus did not affect MBP, CNPase, and GFAP expressions in cuprizone mice. mRNA expression was further confirmed by western blotting.

Discussion

In this study, we demonstrated that olig2 expression was promoted in cuprizone mice. Olig2 silence ameliorated the behavioral changes induced by cuprizone application. Importantly, olig2 silence reversed cuprizone-induced decrease of MBP and CNPase and increase of GFAP in the cortex. These results suggest that oilg2 serves as an important therapeutic target for schizophrenia-like symptoms.

There are still no effective approaches to prohibit the development and progression of schizophrenia. The available symptom-relieving compounds have ameliorated some sufferings of patients [21,22], however, drug development is still restricted by the unknown mechanisms of schizophrenia. A number of animal models have been established to investigate the mechanisms for schizophrenia, the cuprizone model

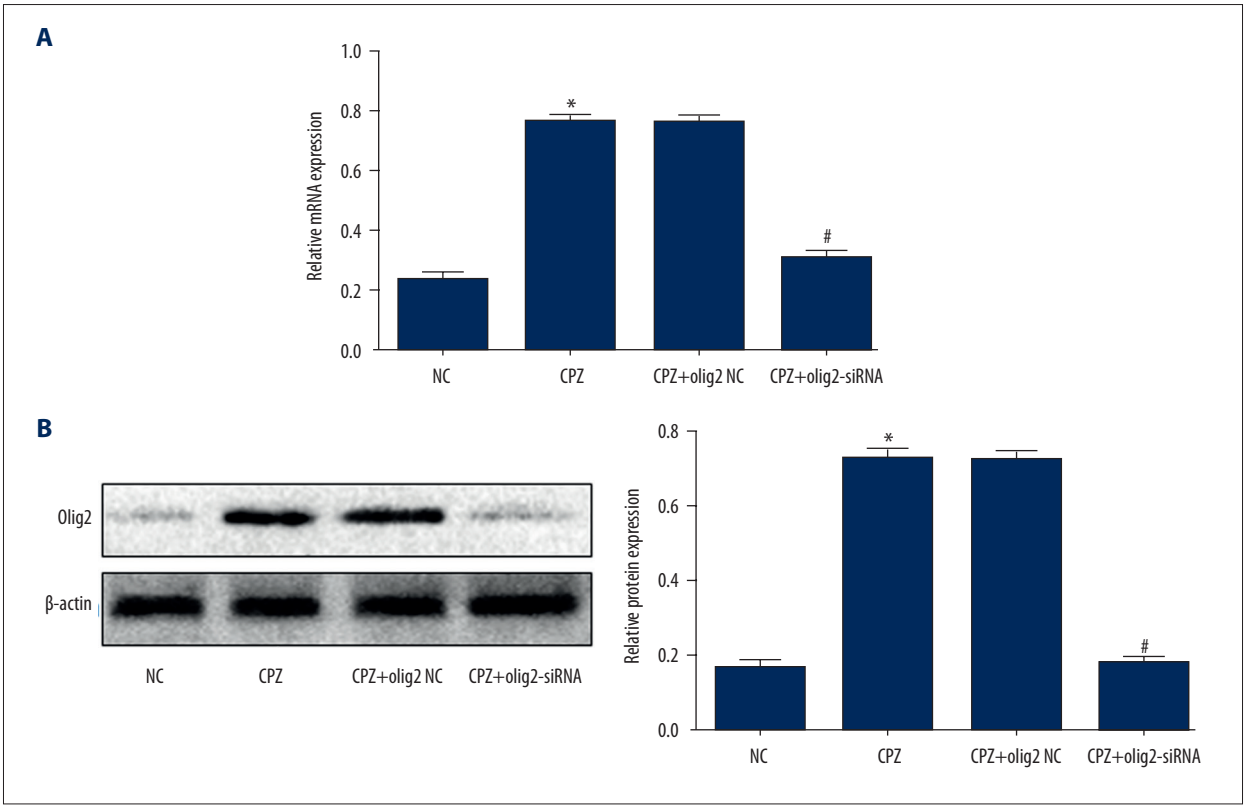

Figure 3. Olig2 silence decreases olig2 expression in cuprizone mice. (**A**) Protein expression; (**B**) mRNA expression. * $p<0.05$ compared with control; # $p<0.05$ compared with CPZ+olig2 NC group.

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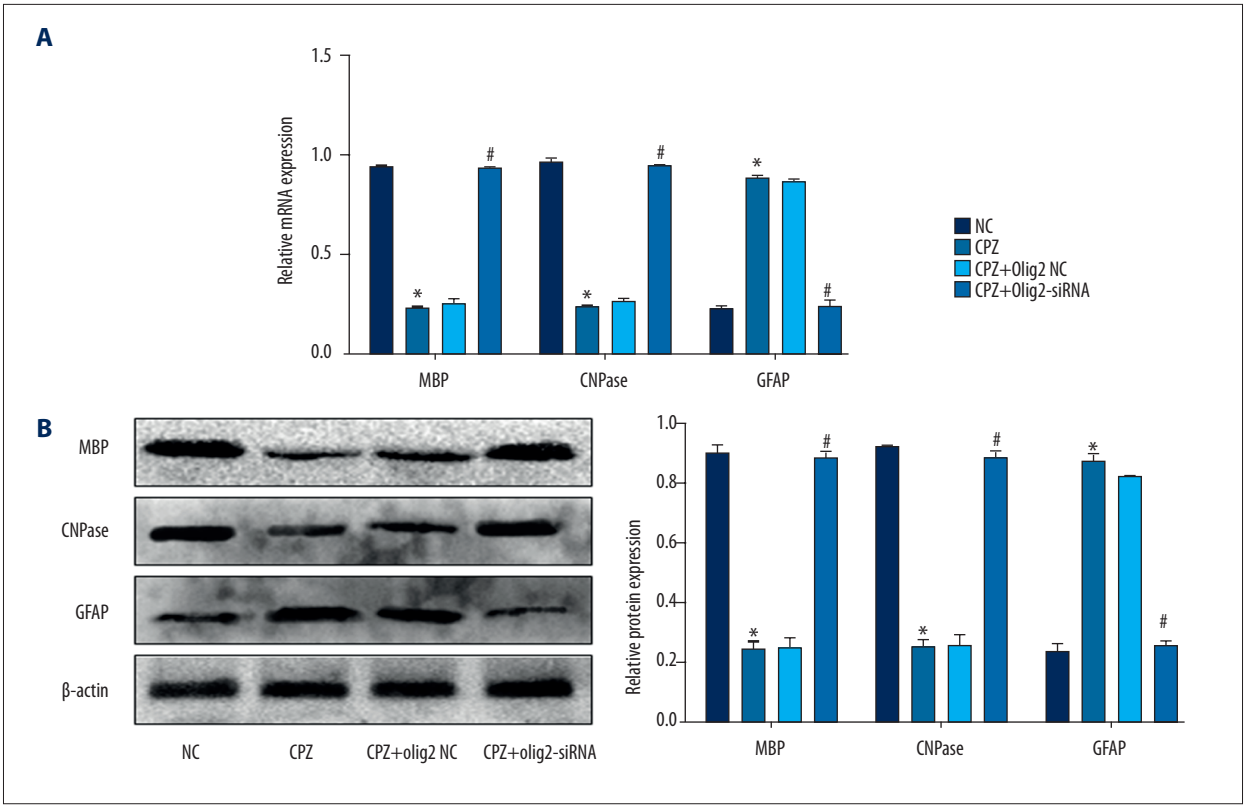

Figure 4. Olig2 silence increases MBP and CNPase, but decreases GFAP expression in cuprizone mice. (**A**) mRNA expression; (**B**) protein expression. * $p<0.05$ compared with control; # $p<0.05$ compared with CPZ+olig2 NC group.

uses the application of a chemical compound (cuprizone) to model schizophrenia-like symptoms [12,23–25]. Cuprizone is a highly selective copper chelating agent, which is neurotoxic and can cause demyelination in the central nervous system [26,27]. In this present study, we treated the mice with a 0.2% cuprizone diet for six weeks. Open-field test and EPM were applied to detect anxiety-like activity and spontaneous activity when the mice were exposed to a new environment. Our data demonstrated that the mice treated with cuprizone preferred to stay in the border area in the open field test and spent more time in the open arm as evidenced in the EPM test. These abnormal behavioral activities revealed that the mice in the model group displayed anxiety-like action, which is a typical characteristic of schizophrenia. Corpus callosum is a damaged region in schizophrenia [28]. Therefore, our data suggest that a cuprizone-induced mice model is an effective model to study schizophrenia-like activity. Although the core symptoms for schizophrenia should also include prepulse inhibitions, anxiety, impaired spatial memory, and interest in social novelty, it is important to note that anxiety and depression are the most frequently reported early signs and symptoms of schizophrenia. It is important to note that we did not find impairment of spatial memory in our cuprizone-induced mice model (data not shown).

A lot of chemical components, including quetiapine, clemastine, and areca catechu extract have been reported to prevent cuprizone-induced schizophrenia-like symptoms [12,26,29]. Olig2 is widely expressed in the central nervous system and plays important roles in the regulation of the development of precursor cells in the ventral neuroectoderm [30]. Additionally, olig2 is a necessary factor for development for oligodendrocytes and motor neurons and also determines the fate of subtypes of those cells. While olig2 is rarely expressed in normal brain tissue, this protein has been found to be promoted in the injured brain [30]. In our study, olig2 expression was remarkably promoted in our cuprizone-induced mice model. In our experiments, we designed olig2 silence virus to block expression of olig2 in the brain. Interestingly, olig2 silence ameliorated cuprizone-induced abnormalities of anxiety-like symptoms. The cuprizone-treated mice with olig2 silence spent more time in the center area compared with the model group. These data suggest that olig2 is the major protein responsible for the behavioral changes in the cuprizone mice. Besides the treatment by chemical components, our study, and others studies [31,32], also suggest that genetic methods might be more specific for the treatment of schizophrenia

Activation of oligodendrocytes is a characteristic of schizophrenia [33,34]. In our study, we found that cuprizone treatment

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promoted olig2 expression. In a previous study, the density of olig2-immunoreactive cells was significantly decreased in subjects with schizophrenia [18]. However, olig2 expression was not altered in the grey or white matter as reported by Mitkus et al. [17]. However, it is important to note that a chemical schizophrenia model might be different from a genetic schizophrenia model. In our study, GFAP was also upregulated after six-weeks of cuprizone treatment. Our data were consistent with previous published reports that cuprizone treatment activated astrocytes [24]. By contrast, in our study, MBP expression was decreased after cuprizone treatment. As MBP is the marker for oligodendrocytes [24], our data further suggest that cuprizone treatment decreased the numbers of oligodendrocytes. Additionally, olig2 silence reversed the changes of these proteins caused by cuprizone. These data suggest that olig2 was required for astrocyte activation and cell loss of oligodendrocytes.

CNPase is one of the important components of the enzyme involved in the synthesis of myelin [35]. In our study, we also detected CNPase expression in both mRNA and protein levels. Our data showed that cuprizone treatment eliminated CNPase expression, which was reversed by olig2 silence. Previous reports suggest that olig2 expression was facilitated and olig2 was transferred to cytoplasm in some of the cells when progenitor cells began to differentiate into GFAP-positive cells [36]. Olig2 has been shown to be upregulated when the brain was damaged [37]. Our data showed that cuprizone treatment leads to increased olig2 expression, but also the increase in expression of GFAP. Therefore, olig2 is not only associated with oligodendrocyte differentiation, but also related to the activation of astrocytes.

Conclusions

In conclusion, cuprizone-induced neurobehavioral changes involved olig2 upregulation. The silence of olig2 could prevent changes, likely through regulating MBP, CNPase, and GFAP expressions.

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