I:C-control and poly I:C-YGS mice in the training session (Fig. 3A, $p > 0.05$). In the retention session, the rate of time exploring the novel object was lower in poly I:C-control mice than either PBS-control or poly I:C-YGS mice (Fig. 3B, $p < 0.05$, respectively). As Hashimoto et al. reported, the cognitive deficits with NORT might show negative symptoms, such as social withdrawal, that are related to cognitive deficits.[24] Therefore, YGS might improve negative symptoms of schizophrenia.

Total glutathione level was restored to a normal level by YGS treatment in poly I:C-mice

Glutathione is a small protein composed of three amino acids (cysteine, glutamate and glycine). Glutathione attenuates external or internal stress by scavenging free radicals and other reactive species and plays a critical role in defense against oxidative stress. Since glutathione levels were decreased in the medial prefrontal cortex and cerebrospinal fluid in schizophrenic patients,[15] we analyzed total glutathione levels in PBS-control mice and poly I:C-control mice. The glutathione level was lower in the whole brain of poly I:C-control than PBS-control mice (Fig. 4, $p < 0.05$). The total glutathione level in poly I:C-YGS mice was significantly increased from that of poly I:C-control mice (Fig. 4, $p < 0.05$) to a comparable level to that of PBS-control mice (Fig. 4, $p > 0.05$).

Discussion

YGS is a traditional herbal medicine and consists of seven different extracts, namely, Atractylodes lancea rhizome, Poria sclerotium, Cnidium rhizome, Uncaria thorn, Japanese Angelica root (Angelica radix), Bupleurum root and Glycyrrhiza in the proportions of 4:4:3:3:3:2:1.5.[16] Liao et al. reported Angelicae radix exerts effects on γ-aminobutyric acid receptors and serotonin receptors.[17] YGS is likely to have effects on not only BPSD of dementia, but also undesirable symptoms of borderline personality disorder and schizophrenia. Therefore, in the present study, we analyzed the effects on a mouse model of schizophrenia, that is poly I:C-mice.

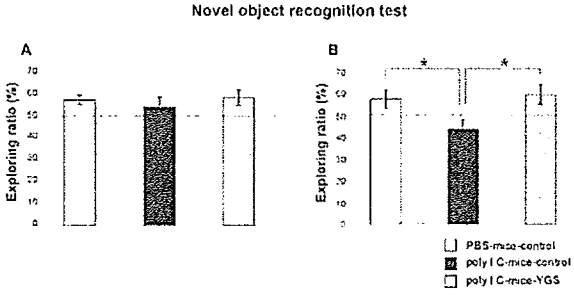

Figure 3. NORT. The rate of time spent exploring the two objects was not different in PBS-control, poly I:C-control and poly I:C-YGS mice in the training session (A). In the retention session, the rate of time exploring the novel object was lower in poly I:C-control mice than either PBS-control or poly I:C-YGS mice (B,*; $p < 0.05$).

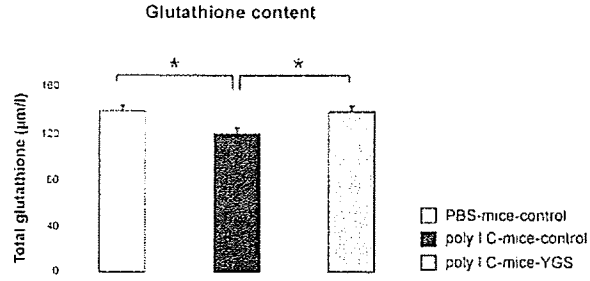

Figure 4. Total glutathione content of poly I:C-control mice was decreased compared to PBS-control mice (*; $p < 0.05$). YGS reversed the decrease in total glutathione content of poly I:C-control mice to the level of PBS-control mice (*; $p < 0.05$).

Poly I:C-mice shows schizophrenia-like symptoms, decreased PPI and increased sensitivity to methamphetamine,[10,12,13] but the basal locomotor activity is comparable to PBS-mice.[11] In the present study, the locomotor activity of poly I:C-mice was also comparable to PBS-mice and YGS did not influence the activities of poly I:C-mice (Figs. 2A, 2B). This data is intriguing because the sedative effect of antipsychotics causes some clinical problems. The decreased PPI, increased sensitivity to methamphetamine and cognitive deficits in poly I:C-mice reverted to control levels after the administration of YGS (Figs. 1, 2, 3). These results suggest that YGS could have therapeutic effects equivalent to established antipsychotics without unwanted sedation in humans, as is the case with poly I:C-mice, although we have not examined whether YGS had sedative effect on PBS mice (control mice) in the present study. This point should be clarified before YGS is brought to clinical trial on schizophrenic patients.

Previous studies have shown that YGS attenuated 5-HT_{2A} receptor agonist-induced behavior[18] and that dopamine receptors and serotonin

receptors were involved in PPI.[19-22] And, in the present study, YGS also improved cognitive deficits in NORT. Previously, Hashimoto et al. reported that phencyclidine-induced cognitive deficits in NORT were improved by subchronic administration of either clozapine or α7 nicotinic receptor agonist, but not of haloperidol.[23,24] Although the mechanisms of the deficit and the improvement of cognitive functions in NORT are not known, it might be related to the function of NMDA receptor because the modulation of NMDA receptor functions could be involved in behavioral alterations of phencyclidine-injected mice and poly I:C-mice[25] and the action mechanism of clozapine and α7 nicotinic receptor agonist.[24,26,27] Additionally, a component of YGS, Uncaria rhynchophylla, has protective effect against apoptosis induced by N-methyl-D-aspartate in rat hippocampal slice.[28] Therefore, the therapeutic effects of YGS on the abnormal behavior of poly I:C-mice could be achieved in part by modulating dopamine, serotonin or glutamate signaling pathways. Since YGS consists of multiple herbal extracts, further studies are required to clarify which compound(s) have therapeutic activities.

Glutathione levels were decreased in the medial prefrontal cortex and cerebrospinal fluid in schizophrenic patients[15] and gene expression of glutathione-synthesizing enzymes and glutathione component in fibroblasts from schizophrenic patients was also decreased.[14] In red blood cells from schizophrenic patients, antioxidant enzyme activities were decreased compared with the control group.[29] Consistent with human studies mentioned above, we also found decreased glutathione levels in the whole brain of poly I:C-mice. YGS significantly restored the decreased total glutathione level (Fig. 3). As a glutathione precursor, N-acetyl-cysteine, improved mismatch negativity in schizophrenic patients[30] and reversed working memory deficits caused by phencyclidine.[31] The therapeutic effects of YGS observed in the present study may be, at least partly, attributed to recovered glutathione synthesis. It remains to be investigated whether upregulation of glutathione levels by a glutathione precursor could restore abnormal behaviors in poly I:C-mice.

The present study showed for the first time that Chinese herbal medicine, YGS, restores behavioral alterations and a decrease of brain glutathione level in schizophrenic model mice. These results suggest that YGS could be a novel remedy for the symptoms of schizophrenia.

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Disclosure

The authors report no conflicts of interest.

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