Role of glyoxalase 1 in methylglyoxal detoxification—the broad player of psychiatric disorders

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ABSTRACT

Methylglyoxal (MG) is a highly reactive α-ketoaldehyde formed endogenously as a byproduct of the glycolytic pathway. To remove MG, various detoxification systems work together in vivo, including the glyoxalase system, which enzymatically degrades MG using glyoxalase 1 (GLO1) and GLO2. Recently, numerous reports have shown that GLO1 expression and MG accumulation in the brain are involved in the pathogenesis of psychiatric disorders, such as anxiety disorder, depression, autism, and schizophrenia. Furthermore, it has been reported that GLO1 inhibitors may be promising drugs for the treatment of psychiatric disorders. In this review, we discuss the recent findings of the effects of altered GLO1 function on mental behavior, especially focusing on results obtained from animal models.

1. Introduction

Methylglyoxal (MG) is a highly reactive α-ketoaldehyde formed endogenously as a byproduct of the glycolytic pathway either by the degradation of triphosphates or by nonenzymatic fragmentation of sugar [1]. MG accumulates under conditions of hyperglycemia, impaired glucose metabolism, or oxidative stress. Excess MG formation causes mitochondrial impairment and reactive oxygen species production, which further increases oxidative stress. MG also reacts with proteins, DNA and other biomolecules, leading to the formation of advanced glycation end products (AGEs) [2,3]. These imply that accumulation of MG causes damage to various tissues and organs [4], resulting in aging and diabetic complications, such as neuropathy, retinopathy, and ischemic heart disease. In addition, AGEs, formed by MG, induce aberrant inflammation by binding to receptors for AGEs, which play a role in chronic inflammation and Alzheimer’s disease [5,6].

To remove MG, various detoxification systems work together in vivo. The glyoxalase system, comprising two enzymes, glyoxalase (GLO) 1 and GLO2, is an enzymatic pathway that catalyzes the glutathione-dependent detoxification of MG (Fig. 1). GLO1 catalyzes the conversion of the hemithioacetal formed by the non-enzymatic reaction of glutathione with MG to S-α-lactoylglutathione, which is then converted to α-lactate by GLO2 [1,7]. GLO1 and GLO2 are ubiquitously expressed in various tissues, including the brain, and provide an effective defense against MG accumulation. Furthermore, DJ-1, aldo-keto reductase, and aldehyde dehydrogenase are also known as enzymes with MG removal activity, and these enzymes work in concert with GLO1 and GLO2 to protect against MG-induced cytotoxicity [8-12].

To date, studies of the MG detoxification system have mainly been conducted in fields related to physical disorders, such as diabetes and renal dysfunction. However, recent years have shown an increased interest in the role of GLO1 and its clinical applications in mental illness. In the present review, we summarize the latest findings on the effects of altered GLO1 function on mental behavior, focusing on the findings from animal models.

2. Clinical studies

A C419A single nucleotide polymorphism (SNP) (reported in dbSNP as rs2736654 or rs4746; NM_006708.3:c.332A>C, p.Glu111Ala) present...
in GLO1, which causes an Ala111Glu substitution in the protein, has been reported to be associated with panic disorder [13] and autism [14, 15]. Junaid et al. reported that the GLO1 enzymatic activity in the autopsied brains of patients with autism was 38% lower than that in healthy controls, and an accumulation of AGEs was also found in the brains of autistic patients [14]. Another clinical study also reported that the GLO1 enzymatic activity was decreased in autistic patients with the A419 allele [16]. Interestingly, another study found that the C419A SNP might affect alternative splicing in GLO1, probably leading to a change in GLO1 enzymatic activity [17].

However, contrary to these reports, some clinical studies have demonstrated no association between C419A SNP and autism [18–20]. One clinical study even reported an association between the C419 allele, instead of A419, and autism, and found lower GLO1 enzymatic activity in autistic patients with the C419 allele than in those with A419 [21]. Consistent with these findings, our research showed that GLO1 enzymatic activity was decreased in schizophrenia patients with the C419 allele, compared with those with A419, although there is no significant change in enzymatic activity between GLO1 with A419 and with C419 using recombinant proteins [22]. We have reported that several patients with schizophrenia have a novel heterozygous frameshift P122fs (rs754100427; NP_006699.2;p.Pro122fs) and an A419C SNP in GLO1, resulting in 40–50% and 15–20% reductions in enzymatic activity, respectively [22]. The frameshift mutation P122fs has also been reported by another group [23]. Moreover, synchrotron radiation nanotomography of the structures of cerebral tissues of the anterior cingulate cortex revealed that a schizophrenia patient with the frameshift P122fs in GLO1 showed marked differences in the curvature of neurites, compared with healthy controls [24]. Another group recently reported that significant differences in GLO1 mRNA expression and enzymatic activity were found in the peripheral blood of first-onset antipsychotic-naïve patients with schizophrenia and controls, and that receiver operating characteristic (ROC) curve analysis showed that GLO1 could predict schizophrenia risk (mRNA, \( P = 4.75 \times 10^{-6} \); enzymatic activity, \( P = 1.43 \times 10^{-7} \)) [25]. A clinical study found MG accumulation in the peripheral blood of a subgroup of patients with schizophrenia [26]. These findings suggest that the decrease in GLO1 activity and subsequent accumulation of MG are involved in the pathogenesis of schizophrenia. Additionally, reduced Glo1 mRNA expression was also observed in major depressive and bipolar disorder patients in a current depressive state, whereas no correlation was observed in a remissive state [27]. This indicated that Glo1 expression level was inversely proportional to the severity score on the Hamilton Depression Rating Scale, suggesting that decreased GLO1 expression might be related to pathophysiology of depression disorder.

However, it is also important to note that recent genome-wide association studies (GWASs) have not shown single nucleotide variants (SNVs) near the GLO1 gene as being relevant to psychiatric diseases. A genome-wide meta-analysis demonstrated the association between an SNV in the GLO1 gene and major depression disorder in males, but there was no genome-wide significance [28]. It should be noted that the results of the clinical studies described above are based on a very limited number of samples, and the results of the genetic analysis of GLO1 may be false positives. In fact, GWASs, case-control studies, and meta-analysis studies have reported no association between SNVs in the GLO1 gene and psychiatric disorders [18,20,29].

We have yet to obtain consistent results regarding the relationship between SNVs in GLO1 and psychiatric disorders. However, the finding that GLO1 enzymatic activity is decreased in patients with psychiatric disorders is likely to be consistent. For example, it is necessary to consider not only the SNVs in GLO1 and its gene expression, but also the effects of environmental factors, including levels of zinc as a cofactor [30] and phosphorylation of T107 in GLO1 [31], and treatment with psychotropic drugs on the enzymatic activity of GLO1. Thus, rather than discussing the SNVs, it is more important to discuss the relationship between reduced GLO1 activity and psychiatric disorders.

3. Animal models

3.1. Anxiety

A number of studies have reported an association between Glo1 expression and anxiety-like behavior in rodents. Table 1 summarizes the findings of mouse models in which Glo1 expression has been experimentally manipulated. First, using a combination of behavioral analysis of six inbred mouse strains and quantitative gene expression, Hovatta et al. demonstrated that there was a statistically significant positive correlation between anxiety-like behavior and Glo1 expression as well as...
Glo1 expression in mice on a transgenic bacterial artificial chromosome [36] and overexpression of Glo1 only in neurons displayed enhanced anxiety-like behavior [37]. Consistent with these findings, treatment with a Glo1 inhibitor reduced anxiety-like behavior [36,38–40], as summarized in Table 2. Glo1 knockout (KO) mice have also been reported to exhibit less anxiety-like behavior [41]. These findings suggest that increased Glo1 expression in neurons enhances anxiety-like behavior in mice.

Since Glo1 degrades MG, a decrease in Glo1 expression or activity would result in an increase in MG levels in the brain. Consistent with the findings that a decrease in Glo1 expression is associated with a decrease in anxiety, several studies have reported that anxiety is reduced in MG-treated mice [36,42]. The behavioral changes in MG-treated animals are summarized in Table 3. Since the intracerebroventricular administration of Glo1 in mice on a transgenic bacterial artificial chromosome [36] and overexpression of Glo1 only in neurons displayed enhanced anxiety-like behavior [37]. Consistent with these findings, treatment with a Glo1 inhibitor reduced anxiety-like behavior [36,38–40], as summarized in Table 2. Glo1 knockout (KO) mice have also been reported to exhibit less anxiety-like behavior [41]. These findings suggest that increased Glo1 expression in neurons enhances anxiety-like behavior in mice.

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of MG into the brain also reduces anxiety [43,44], the effect of this MG administration is thought to have a direct effect on the central nervous system. Furthermore, McMurray et al. reported reduced anxiety with the administration of microinjection of MG into the basolateral amygdala, a well-known region of brain responsible for anxiety [37]. Additionally, contrary to the findings so far, several reports have shown that Glo1 expression is high in mice with low anxiety [44–47]. However, even in these mice, MG levels and MG-derived AGEs were found to be high in the brain [44], indicating that there is a consensus on the relationship between increased MG and reduced anxiety. Regarding the reason why the low-anxiety mice showed high MG levels instead of elevated Glo1 expression, the authors presumed that the low-anxiety animals were primarily selected for high concentrations of MG and that selection of mice with elevated expression of Glo1 as well, which is protective against AGE formation, was expected [44]. Thus, the finding is also consistent with those of other studies in that the increase in MG decreases anxiety, although it may contradict them in terms of the amount of Glo1 expression. This is consistent with our hypothesis that the decrease in Glo1 activity and subsequent increase in MG levels, rather than SNVs and expression within the Glo1 gene, should be the focus.

However, does MG suppress anxiety-like behavior? A recent study provides a possible answer to this question: MG is a partial agonist to the GABAA receptor [36]. It has been electrophysiologically confirmed that MG directly activates the GABAA receptor, leading to the suppression of anxiety-like behavior in mice. These findings suggest that MG can act as an anxiolytic through GABAA receptor activation, similar to benzodiazepines. Thus, it is suggested that high Glo1 expression can reduce MG concentration in the brain, thereby decreasing the activity of the GABAA receptor, resulting in enhanced anxiety-like behavior.

Contrary to these findings, STZ-treated rats [48,49] and Akita mice [50], which are models of type 1 diabetes, showed high anxiety with decreased Glo1 expression and accumulation of MG-derived proteins in the brain. In addition, rats that were fed a high-salt diet showed decreased Glo1 expression in the amygdala and hippocampus and enhanced anxiety-like behavior [51]. Moreover, perinatal administration of methylmercury reduces hippocampal expression of Glo1 and enhances anxiety [52]. Various rodent disease models with altered gene expression of Glo1 are summarized in Table 4. However, there are no data to show that the decrease in Glo1 expression and subsequent MG accumulation directly affect the enhanced anxiety exhibited in these animal models. We cannot rule out the possibility that anxiety in these animal models was triggered by other factors that had a greater impact than decreased Glo1 expression. Therefore, to clarify whether Glo1 expression is involved in anxiety in other disease models, rescue experiments by direct manipulation of Glo1 gene expression and MG administration would be necessary. Furthermore, measurement of Glo1 activity and quantification of MG levels in the brain are important to clarify the role of Glo1 in these pathological models.

### 3.2. Depression

GLO1 inhibitors have been reported to be useful as novel antidepressants [39]. Two structurally distinct GLO1 inhibitors (S-benzylglutathione cyclopentyl diester or methyl-gerfelin) ameliorated depression-like behavior in a rodent model after 5 days of treatment, whereas an existing antidepressant, fluoxetine, takes 14 days of treatment to ameliorate depression-like behavior. Furthermore, the 5-day treatment with GLO1 inhibitors induced molecular markers of the antidepressant response, including brain-derived neurotrophic factor and cyclic-AMP response-binding protein phosphorylation in the hippocampus and medial prefrontal cortex. These findings are also supported by a report showing that Glo1 is one of the genes contributing most to the antidepressant response [53]. Thus, GLO1 inhibitors may be effective as novel and fast-acting drugs for treating depression.

In contrast, several reports have shown that MG-treated mice exhibit depression-like behavior [42,54]. In addition, rodents models of depression induced by chronic mild stress [55] and social defeat stress [56,57] showed depression-like behaviors with decreased Glo1 expression in the brain. Furthermore, we have shown that Glo1 KO mice showed no accumulation of MG in the brain, although Glo1 KO mice
exhibit antidepressant-like behavior [58]. This result is supported by in vitro and in vivo studies showing that in the absence of GLO1, aldol-keto reductase may compensate for MG detoxification, resulting in no MG accumulation [9,10]. Another group also reported that Glo1 KO induced no accumulation of MG-H1, an MG-derived AGE, in the brain [41].

Thus, further studies are required to evaluate the pharmacological mechanisms underlying the antidepressant effects of GLO1 inhibitors. For example, the molecular mechanism underlying the anxiolytic and antidepressant-like effect of GLO1 inhibitors is thought to be due to GABA_A receptor stimulation by accumulated MG [39], but there is still no direct evidence that decreased GLO1 activity actually stimulates the GABAergic system in the brain, including the hippocampus and prefrontal cortex, through MG accumulation, leading to low levels of anxiety. In addition, since a previous study reported that Glo1 KO mice showed antidepressant-like behavior in the forced swimming test even though there was no MG accumulation [58], it is necessary to examine how GLO1 inhibitors could reduce MG levels in the brain. We believe that it is also necessary to consider the possibility that the administration of GLO1 inhibitors improved depression-like behavior without the pharmacological effects of MG.

### 3.3. Schizophrenia

As mentioned above, we have reported that several patients with schizophrenia have a novel frameshift mutation and SNP in GLO1 that results in reductions in enzymatic activity [22]. To elucidate the impact of loss of function of GLO1 on the pathogenesis of schizophrenia, we generated Glo1 KO mice and evaluated their behavioral phenotypes [59]. However, the Glo1 KO mice did not show schizophrenia-like behavior, and the MG levels in the brain remained unchanged.

Next, we sought to develop a novel model for schizophrenia with an add-on treatment of an environmental factor, vitamin B6 (VB6) deficiency, observed in patients with schizophrenia [22,59,60], in Glo1 KO mice. VB6 is known as a carbonyl scavenger that detoxifies MG [61,62]. We previously found that VB6 levels in the peripheral blood of schizophrenia patients with GLO1 dysfunction were significantly lower than those in healthy controls [22]. More than 35% of patients with schizophrenia have low levels of VB6 (clinically defined as male, < 6 ng/ml; female, < 4 ng/ml). Various other studies have reported similar results [63,64]. VB6 levels are inversely proportional to the severity score on the Positive and Negative Syndrome Scale [60]. Moreover, a recent review has shown that decreased VB6 in patients with schizophrenia is the most convincing evidence of peripheral biomarkers for major mental disorders [65]. Moreover, we recently reported that VB6-deficient mice showed an enhanced noradrenergic system in the brain, leading to social deficits and cognitive impairment comparable to the negative symptoms and cognitive impairment seen in patients with schizophrenia [56]. Based on these findings, we depleted VB6 in Glo1 KO mice by feeding them VB6-lacking diets to develop a mouse model that further recapitulates the pathology of schizophrenia. We demonstrated that MG accumulated in the brain of Glo1 KO mice with VB6 deficiency (KO/ VB6 (−)), and that these mice exhibited schizophrenia-like behaviors, such as a sensorimotor deficit in the prepulse inhibition test [58]. These findings suggest that Glo1 deletion alone is insufficient to increase MG levels in the brain, and MG accumulation in the brain occurs only when another MG detoxification is deficit, such as VB6 deficiency. In fact, we could also confirm the accumulation of MG-H1, an MG-derived AGE, in the brains of KO/VB6(−) mice [67].

Furthermore, we found aberrant gene expression related to mitochondrial function and respiratory deficits in the mitochondria of KO/ VB6(−) mice. Moreover, we found higher expression of oxidative stress markers as a result of mitochondrial dysfunction. MG can also disrupt mitochondrial respiration; incubation of isolated mitochondria with MG produced a concentration-dependent decrease in state III, as well as an increase and then a decrease in state IV respiration [68]. These findings suggest that mitochondrial dysfunction can be caused by aberrant gene expression related to mitochondria and MG accumulation. Our findings are consistent with the result that GLO1 KO-hiPSC-derived neurons show mitochondrial dysfunction and MG-H1 accumulation after MG treatment [69].

Mitochondrial dysfunction has frequently been reported in patients with schizophrenia [70]. Several studies using postmortem brains demonstrated a decrease in the activity of complex IV in the PFC of
patients with schizophrenia [71], and a global downregulation of mitochondria-related genes by microarray analysis [72]. Mitochondrial dysfunction has also been observed in patient-derived IPS cells [73,74]. These findings suggest that the combination of GLO1 dysfunction and VB6 deficiency may affect mitochondrial function in KO/VB6(−) mice, causing schizophrenia-like sensorimotor deficits. Mitochondrial dysfunction has been observed in many psychiatric disorders, including depression [75], autism [76], anxiety disorders [77], and epilepsy [78]. Thus, this may be a common molecular basis for psychiatric disorders. In a mouse model of schizophrenia, as well as other physical disorders, MG accumulation was found to have adverse effects on brain function. Considering the molecular mechanism revealed in this study, GLO1 inducers, such as trans-resveratrol and hesperatin [79], rather than inhibitors and VB6 supplementation [80] may be effective as a new therapeutic strategy for schizophrenia patients with GLO1 dysfunction and VB6 deficiency.

3.4. Other psychiatric and neurological traits

A recent study on prenatal treatment with valproic acid (VPA) in a mouse model of autism showed enhanced GLO1 expression and reduced MG levels in the brain [81]. Furthermore, GLO1 inducers ameliorated the autism-like phenotype in VPA-treated mice through GABA_B2 stimulation by MG. These findings are not consistent with the clinical findings that GLO1 enzymatic activity was decreased, and AGE accumulation was found in the autopsied brains of patients with autism [14]. The reason for this disagreement may be secondary effects unrelated to the autistic pathology caused by prenatal VPA administration. In addition, the possibility that the decreased GLO1 activity observed in patients with autism reflects secondary effects of the onset of autism may need to be considered.

The GABA_B2 agonistic activity of MG has also been reported to have antiepileptic and alcohol detoxification effects, such as benzodiazepine. Pretreatment with MG attenuated pilocarpine-induced seizures at both behavioral and electroencephalogram levels [81]. Pretreatment with a GLO1 inhibitor also alleviated pilocarpine-induced seizures, whereas Glo1 overexpression exacerbated seizures and decreased the MG concentration in the brain. Likewise, GLO1 inhibitors reduced alcohol consumption [82,83] and handling-induced convulsion after alcohol injection [84], whereas Glo1 overexpression exacerbated these effects. In addition, alcohol consumption was reduced in Glo1 hemizygous-knockdown mice [82]. Although there are no clinical reports showing an association between alcoholism/sleep disorder and GLO1, a clinical study reported that rs1049346 T>C SNP in 5′-UTR of GLO1 was associated with late-onset epilepsy and drug-resistant epilepsy [85]. The C allele increases GLO1 enzymatic activity in whole blood cells [86]. These findings are consistent with the results of rodent studies.

4. Summary

According to the present review, the expression and activity of GLO1 in the brain may be involved in the pathogenesis of various psychiatric disorders. In contrast to the effects on physical diseases, the various GABA_B2 receptor-mediated effects of MG, such as anxiolytic and antidepressant effects, associated with suppression of GLO1 function, are brain-specific effects. To clarify the effects of GLO1 on brain function and the development of psychiatric disorders, it is necessary to clarify the relationship between GLO1 activity and psychiatric disorders in clinical studies with large sample sizes and to examine in detail the molecular mechanisms by which increased GLO1 activity leads to anxiety and depression in studies involving mouse models.

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Declaration of competing interest

The authors have declared that no conflict of interest exists.

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