A Challenging Story of Schizophrenia and Glutathione

Subjects: Biology

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Schizophrenia (SZ) is a devastating mental illness with a complex and heterogeneous clinical state. Oxidative stress, and in particular glutathione (GSH) dysregulation, has been demonstrated to play a crucial role in SZ pathophysiology. In fact, glutathione is a leading actor of oxidative-stress-mediated damage in SZ and appears to reflect the heterogeneity of the disease.

Keywords: schizophrenia ; glutathione ; oxidative stress ; neurodegeneration ; biomarker

1. Introduction

Schizophrenia is one of the most serious and debilitating psychiatric illnesses [1][2][3], characterized by three groups of symptoms: positive, negative and cognitive symptoms. Positive symptoms consist of hallucinations (perceptions in the absence of an external stimulus) and delusions (fixed and false beliefs arising internally). Negative symptoms include decreased emotional expression, amotivation, apathy and social withdrawal. Impaired cognitive functions involve disorganization of thought, deficit in long-term memory and sustained attention, problems in processing speed [4]. The psychiatric diagnosis of SZ remains centered on the analysis of clinical symptoms, as the pathophysiology of the disorder is still unclear, and there is a lack of appropriate biomarkers. Many alternative hypotheses have been formulated regarding the pathologic mechanisms of SZ, whose developmental and neurodegenerative nature is still a matter of debate [5]. The pathogenic pathways include, among others: impaired neurotransmission, neuroinflammation, autoimmune dysfunctions, oxidative stress, defects of myelination [6]. Although the suggested mechanisms are multiple and disparate, the general idea is that they may converge on a common pathway [7]. One of the candidates for this process is oxidative stress [8]. Several studies suggested a role for oxidative stress in the molecular mechanisms involved in the disease etiology. Evidence for oxidative damage, including decreased levels of antioxidants and in particular reduced glutathione (GSHr) and total glutathione (GSHt, that is the sum of GSHr and its oxidized form GSSG), has been found in body fluids and postmortem brain tissues of patients affected by SZ [9][10][11].

2. Oxidative Stress and Glutathione

Oxidative stress is caused by an imbalance between the excessive production of reactive oxygen species (ROS) and the cellular antioxidant defense, which is usually able to counteract the reactive compounds and repair the resulting injury [12]. The ROS production occurs inside the cell during normal aerobic metabolism and mainly for mitochondrial respiration with its consequent incomplete reduction in oxygen to water. ROS include both free radicals (containing highly reactive unpaired electron), such as: superoxide ($O_2^{-\cdot}$) and hydroxyl radical ($OH^{\cdot}$), and other molecular species, like hydrogen peroxide (H_2O_2). Prolonged exposure to these oxidant intermediates determines the oxidation of cellular components (proteins, lipids and DNA). Under normal physiologic conditions, the cell deals with the flux of ROS. Oxidative stress occurs when the ROS level exceeds the antioxidant systems. The brain is a sensitive site of oxidative damage due to its high metabolic rate such that consuming a large amount of inspired oxygen produces many reactive species [13]. In addition, the brain has a low level in antioxidant systems and a reduced capacity for cellular regeneration that worsen its condition. The most prevalent antioxidant in the brain is glutathione, a tripeptide made up of cysteine, glutamate and glycine. It is essential for cellular detoxification of reactive oxygen species in the central nervous system, and oxidative stress together with an altered glutathione metabolism may be implicated in the axonal degeneration observed in various neurodegenerative diseases [14]. Glutathione exists in a reduced state (GSHr) able to scavenge free radicals and in an oxidized state (GSSG) capable of causing protein S-glutathionylation, a process that consists in the connection of mixed disulphide bonds between glutathione and protein cysteine residues (Cys). In GSH metabolism, the oxidation of two molecules of GSHr generates one molecule of GSSG that, in turn, can be reduced back by the enzyme GSH reductase. The ratio between GSHr and GSSG has the function of maintaining the redox balance and potential in the cell, and in normal condition, it is about 100. Under oxidative stress, the GSHr/GSSG ratio decreases to 10 or less, and these values are able to trigger protein S-glutathionylation, which, in turn, can alter the function, interactions and localization of

proteins. The oxidation of Cys residues by ROS can cause irreversible modifications that bring to dangerous dysfunction, thus GSH protects the proteins by reducing their thiols (i.e., their –SH functional groups). More importantly, abnormal protein S-glutathionylation has been considered the cause of several neurodegenerative diseases exacerbating the injury of oxidative stress.

3. Glutathione in Schizophrenia

Growing evidence suggests that the dysregulation of GSH metabolism may have a crucial part in SZ pathophysiology. A huge number of studies report a reduction in GSHr in tissues of SZ patients compared to controls. In GSH metabolism, the GSHr/GSSG ratio and the GSH levels are the primary causes of oxidative balance. It is, in other words, fundamental for the cell to maintain a high GSHr level, a low GSSG level and appropriate GSHt values. In SZ conditions, decreased levels of GSHr and GSHt (generally indicated as relative measures, referred to as either controls or average levels) have been reported in blood, including plasma [11][15][16][17][18][19][20][21], serum [22][23][24][25][26][27][28] and erythrocytes [29][30][31][32], but also in cerebrospinal fluid (CSF) and postmortem brain tissue of patients [9][10][33].

However, there are also data not consistent with the above mentioned results. For example, in the work of Samuelsson and colleagues [34], no differences in plasma and CSF levels of GSH were observed in SZ patients, as compared to controls.

Part of the variability might be due to the different analytical methods and the differences in the processing and/or storage of the biological samples. For example, red blood cells are responsible for the major amount of GSH in the blood, and a slight hemolysis (0.1%–1%) can result in an erroneous high value of GSH in plasma [35][36].

It is also of particular interest to determine whether the GSHr/GSSG ratio, GSHr, GSHt or GSSG levels can correlate to stages, severity and type of symptoms [37]. Many authors suggested that GSH levels may vary according to disease stage (prodromic phase, first episode of psychosis and chronic condition), but this aspect would necessitate further analysis. Nonetheless, the literature reported studies on the diverse phases of the illness, though not all in parallel. Alongside the studies already mentioned and preponderantly obtained in chronic patients, there are works specifically regarding the prodromic stage and first episode of psychosis.

For example, in first-episode psychosis, markers of oxidative damage have been demonstrated to be associated with positive [31] and negative symptoms [38][39] as well as cognitive impairment [40]. More precisely, total GSH and GSHr were decreased, while GSSG increased in FEP [19][27][41][42], indicating that glutathione may be an early indicator of oxidative stress in the course of schizophrenia. Of particular interest is the correlation between GSSG increase and cognitive impairment, which is a common clinical feature of the disease and could thus be due to oxidative-stress-mediated neurodegeneration [43].

Thus, there is considerable evidence of GSH metabolism dysregulation in the different stages of the disease, although findings are not always consistent.

The GSH levels and their relation with the severity of clinical symptoms are also matters of conflicting results. Raffa et al. [44] reported an inverse correlation between the clinical global impression-severity scores and the levels of total GSH and GSHr. In accordance with these results, Tsai et al. [26] also demonstrated a significative negative association of GSH levels with SZ in the acute phase, and the study of Juchnowicz et al. [45] found that GSH could be useful in distinguishing FEP and chronic patients from controls. Overall, some studies showed that GSHr levels are associated with the severity of both positive or negative symptoms [44][46][29][47][48][49][50][51], while others do not observe any association [25][52][42][53][54][55].

4. From the Periphery to the Center

The association between peripheral and central GSH levels in SZ, primarily in its chronic stage, allows us to draw interesting observations. Magnetic resonance spectroscopy (MRS) studies reported a GSH decrease in some SZ-damaged brain areas, such as the anterior cingulate cortex (ACC), thalamus, striatum and medial prefrontal cortex [56][37][57][58][59]. In particular, the consistent decline of GSH levels detected in ACC is confirmed by a metanalysis revision. This result links the peripheral datum in the blood with that in the brain, indicating that peripheral glutathione levels can mirror the brain's oxidative condition. Nevertheless, the same observations have not been always reported in MRS studies involving the same cortical regions.

Many are the variables that could explain the presence of the diverse discrepancies among the MRS studies [60]. The difference in brain areas, the strength of the magnetic fields used (1.5, 3, 4 and 7T) making it difficult to discriminate the spectrum of GSH due to the overlap with other neurochemicals, and the type of acquisition strategy all may affect the final results, in addition to the criteria of patients' selection such as: FEP vs. chronic, and drug-free vs. medicated. The group of Palaniyappan [61] suggested an alternative and interesting hypothesis, positing that the difference in GSH levels could be due, at least partially, to the presence of two subtypes of patients: one with evident GSH deficit and another one with a GSH condition rather comparable to that of controls. These subgroups may differ in disease outcome regarding parameters like disease severity or progression, as well as response to treatments. Hence, the different vulnerability of patients to oxidative stress may account for the diverse MRS results. In addition, it is reasonable to suppose that not all brain areas of interest in neuronal damage in SZ owe their condition directly to oxidative stress, but some of them may rather be affected as a consequence of the oxidative injury of connected areas.

5. N-Acetylcysteine: A Support to GSH Implication in SZ

The implication of GSH in SZ is also supported by preclinical and clinical studies conducted with the antioxidant drug N-acetylcysteine (NAC), which is a precursor of L-cysteine and plays a role as a cysteine donor for GSH synthesis. Preclinical studies showed that its use determined an increase in plasma cysteine levels and a subsequent involvement in rising GSH levels [62]. It has also been shown that NAC penetrates the blood–brain barrier (BBB), augmenting GSH concentration in the brain [63][64]. Works performed in SZ animal models demonstrated that the administration of NAC reverses GSH depletion and behavioral deficit [65][66]. Placebo-controlled trials confirmed that NAC treatment increases glutathione levels in the medial prefrontal cortex in early-phase SZ [67], and several clinical studies found that NAC led to a significant reduction in positive, negative and cognitive symptoms in patients who either underwent antipsychotic therapy or were untreated [68][69][70][71][72][73]. However, the results regarding negative symptoms are more prominent than those of positive symptoms. An intriguing finding is the correlation between the baseline level of GSH and the effect of NAC, as a low level appears associated with a beneficial effect of NAC supplementation mostly on positive symptoms [67][68][69][70][71][72][73][74]. In early-phase SZ, an interesting beneficial effect of NAC administration in protecting white matter integrity has also been discovered, with a six-month treatment that increases the functional connectivity along the cingulum and the fornix [75][76]. This finding collocates glutathione dysregulation in the optic of playing a role in neurodegeneration and provides additional data on the link between glutathione-mediated oxidative stress and white matter impairment in SZ.

6. NMDAR Hypofunction and Its Link to Glutathione in SZ

The two major hypotheses formulated to explain the pathophysiological involvement of GSH in SZ are the N-methyl-d-aspartate (NMDA) receptor (NMDAR) hypofunction, or glutamatergic hypothesis, and the myelination impairment. It has been demonstrated that NMDAR hypofunction acts synergistically with oxidative stress, revealing an interesting SZ pathophysiological mechanism. In adult SZ rodent model systems, both NMDAR hypofunction and oxidative stress induce similar behavioral and cognitive disturbances, suggesting that they may be reciprocally correlated [6][77]. Steullet and colleagues [78] found that GSH deficit determines a reduced NMDAR function in rat hippocampal slices. The hypothesis is that GSH depletion may lead to an alteration of the redox state and to an oxidative modification of redox-sensitive sites of NMDAR. Particularly vulnerable to NMDAR hypofunction are also parvalbumin (PV) interneurons, presumed to be implicated in SZ pathophysiology. The NMDAR contains redox-sensitive active sites located on cysteine residues, and glutathione is able to depress the function of the receptor by oxidizing those sites [79][80]. Moreover, depletion of GSH leads to NMDAR impairment of synaptic plasticity with a decrease in the response and LTP [78][81]. On the other hand, NMDAR hypofunction can reduce GSH levels, contributing to a further redox imbalance. It has also been demonstrated that NMDAR antagonists increase ROS production [82][83][84] and that synaptic activity mediated by NMDAR increases the GSH synthesis, coping with the need of antioxidant requested by neuron activity to avoid oxidative stress [85]. This scenario highlights a reciprocal NMDAR–GSH link. The glutamatergic hypothesis proposes that NMDAR hypofunction governs the damage of PV fast-spiking GABAergic interneurons and their synchronization activity [89], resulting in the diverse SZ symptoms.

Among the neurobiological anomalies derived from oxidative stress and potentially involved in the pathophysiology of SZ, there is also abnormal myelination. In fact, widespread disruption of white matter integrity has been observed in SZ. This pattern of myelination damage is typical in both GCLM-KO mice and SZ patients. The oligodendrocytes and their progenitors are highly susceptible to redox dysregulation. It is known that glutathione depletion causes the death of oligodendrocytes and their precursors [86][87], with a consequent deficit in myelination.

7. Glutathione as a Biomarker for Schizophrenia

The accumulating evidence of GSH involvement in SZ pathophysiology candidate this antioxidant molecule as an SZ biomarker. Given that direct access to the brain is impossible, peripheral tissues such as blood and cerebrospinal fluid are considered good sources for identifying potential biomarkers and molecular mechanisms that underlie SZ. Indeed, there is a significant and constantly growing interest in searching for blood-based biomarkers to assist in the SZ diagnosis. Blood biomarkers are easily accessible, minimally invasive and, at the same time, not expensive, therefore optimal for clinical use. Glutathione could be one of these markers, as it can cross the BBB in its reduced form [88], but a number of controversial outcomes characterize the GSH role in SZ, probably because of the complexity of this mental illness and its great heterogeneity of symptoms. In this scenario, the variability of results regarding the GSH levels in SZ patients may reflect the different disease conditions and may allocate glutathione as a biomarker for the SZ states, where scholars intended for SZ "state" the different groups of symptoms that define the phenotype of a subject (i.e., deficit or non-deficit schizophrenia). To define a biomarker able to distinguish the different states of a complex disease is crucial to favor a correct diagnosis and to drive the treatments in the context of personalized medicine.

Indeed, a wide body of evidence shows a reduction in glutathione levels in plasma and serum of chronic and FEP SZ patients that makes into correlation the dysregulation of GSH metabolism not only with the chronic stage, but also with the initial acute phase of the pathology, suggesting that glutathione could be an early biomarker of SZ.

However, the contradictory results of GSH levels among studies (especially those using MRS) could be explained by a different vulnerability of the brain regions to oxidative damage. Accordingly, a different expression of glutathione in the diverse brain areas has been shown in mouse models, where a higher GSH expression may indicate a condition less prone to oxidative stress. Different human brain regions and subregions likely show different GSH expressions, and a GSH measurement conducted without distinguishing between the diverse areas may lose these differences. Thus, the initial baseline level of glutathione accounting for the propensity to an oxidative insult in the corresponding region should be considered.

8. Conclusions

In conclusion, even if the role of glutathione in the pathophysiology of SZ is largely recognized, the heterogeneity of results poses several problems and reflects not only the disparity of methods used and experimental systems performed among the studies but also the possible influence of the variability in SZ phenotypes, stage and severity of the disease. Therefore, it is believed that this heterogeneity, rather than a mere problem of techniques, is an intriguing puzzle that could redefine the classification of SZ patients. In this scenario, the identification of glutathione as a diagnostic biomarker able to distinguish between patient subtypes leads to a promising and challenging concept, which could pave the way for innovative personalized approaches in the treatment of SZ.

References

1. Jauhar, S.; Johnstone, M.; McKenna, P.J. Schizophrenia. Lancet 2022, 399, 73–486.
2. Tandon, R.; Gaebel, W.; Barch, D.M.; Bustillo, J.; Gur, R.E.; Heckers, S.; Malaspina, D.; Owen, M.J.; Schultz, S.; Tsuang, M.; et al. Definition and description of schizophrenia in the DSM-5. Schizophr. Res. 2013, 150, 3–10.
3. Van Os, J.; Kapur, S. Schizophrenia. Lancet 2009, 374, 635–645.
4. McCutcheon, R.A.; Reis Marques, T.; Howes, O.D. Schizophrenia-An Overview. JAMA Psychiatry 2020, 77, 201–210.
5. Gupta, S.; Kulhara, P. What is schizophrenia: A neurodevelopmental or neurodegenerative disorder or a combination of both? A critical analysis. Indian J. Psychiatry 2010, 52, 21–27.
6. Steullet, P.; Cabungcal, J.H.; Monin, A.; Dwir, D.; O'Donnell, P.; Cuenod, M.; Do, K.Q. Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A "central hub" in schizophrenia pathophysiology? Schizophr. Res. 2016, 176, 41–51.
7. Yao, J.K.; Keshavan, M.S. Antioxidants, redox signaling, and pathophysiology in schizophrenia: An integrative view. Antioxid. Redox Signal. 2011, 15, 2011–2035.
8. Cuenod, M.; Steullet, P.; Cabungcal, J.H.; Dwir, D.; Khadimallah, I.; Klauser, P.; Conus, P.; Do, K.Q. Caught in vicious circles: A perspective on dynamic feed-forward loops driving oxidative stress in schizophrenia. Mol. Psychiatry 2022, 27, 1886–1897.

9. Do, K.Q.; Trabesinger, A.H.; Kirsten-Krüger, M.; Lauer, C.J.; Dydak, U.; Hell, D.; Holsboer, F.; Boesiger, P.; Cuénod, M. Schizophrenia: Glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur. J. Neurosci. 2000, 12, 3721–3728.
10. Gawryluk, J.W.; Wang, J.F.; Andreazza, A.C.; Shao, L.; Young, L.T. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. Int. J. Neuropsychopharmacol. 2011, 14, 123–130.
11. Coughlin, J.M.; Yang, K.; Marsman, A.; Pradhan, S.; Wang, M.; Ward, R.E.; Bonekamp, S.; Ambinder, E.B.; Higgs, C.P.; Kim, P.K.; et al. A multimodal approach to studying the relationship between peripheral glutathione, brain glutamate, and cognition in health and in schizophrenia. Mol. Psychiatry 2021, 26, 3502–3511.
12. Sies, H. Biochemistry of oxidative stress. Angew. Chem. Int. 1986, 25, 1058–1071.
13. Salim, S. Oxidative Stress and the Central Nervous System. J. Pharmacol. Exp. Ther. 2017, 360, 201–205.
14. Aoyama, K. Glutathione in the Brain. Int. J. Mol. Sci. 2021, 22, 5010.
15. Dietrich-Muszalska, A.; Olas, B.; Głowacki, R.; Bald, E. Oxidative/nitrative modifications of plasma proteins and thiols from patients with schizophrenia. Neuropsychobiology 2009, 59, 1–7.
16. Raffa, M.; Mechri, A.; Othman, L.B.; Fendri, C.; Gaha, L.; Kerkeni, A. Decreased glutathione levels and antioxidant enzyme activities in untreated and treated schizophrenic patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 2009, 33, 1178–1183.
17. Raffa, M.; Barhoumi, S.; Atig, F.; Fendri, C.; Kerkeni, A.; Mechri, A. Reduced antioxidant defense systems in schizophrenia and bipolar I disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 2012, 39, 371–375.
18. Raffa, M.; Bel Hadj Youssef, I.; Ben Othman, L.; Fendri, C.; Mechri, A. Concentrations plasmatiques des glutathions et leurs corrélations avec les caractéristiques cliniques et thérapeutiques des patients atteints de schizophrénie [Plasmatic glutathione levels and their relationships with clinical and therapeutic features in patients with schizophrenia]. Encephale 2021, 47, 10–14. (In French)
19. Ruiz-Litago, F.; Seco, J.; Echevarría, E.; Martínez-Cengotitabengoa, M.; Gil, J.; Irazusta, J.; González-Pinto, A.M. Adaptive response in the antioxidant defence system in the course and outcome in first-episode schizophrenia patients: A 12-months follow-up study. Psychiatry Res. 2012, 200, 218–222.
20. Nucifora, L.G.; Tanaka, T.; Hayes, L.N.; Kim, M.; Lee, B.J.; Matsuda, T.; Nucifora, F.C., Jr.; Sedlak, T.; Mojtabai, R.; Eaton, W.; et al. Reduction of plasma glutathione in psychosis associated with schizophrenia and bipolar disorder in translational psychiatry. Transl. Psychiatry 2017, 7, e1215.
21. Guidara, W.; Messedi, M.; Naifar, M.; Maalej, M.; Grayaa, S.; Omri, S.; Ben Thabet, J.; Maalej, M.; Charfi, N.; Ayadi, F. Predictive value of oxidative stress biomarkers in drug-free patients with schizophrenia and schizo-affective disorder. Psychiatry Res. 2020, 293, 113467.
22. Ivanova, S.A.; Smirnova, L.P.; Shchigoreva, Y.G.; Semke, A.V.; Bokhan, N.A. Serum Glutathione in Patients with Schizophrenia in Dynamics of Antipsychotic Therapy. Bull. Exp. Biol. Med. 2015, 160, 283–285.
23. Vidović, B.; Stefanović, A.; Milovanović, S.; Đorđević, B.; Kotur-Stevuljević, J.; Ivanišević, J.; Miljković, M.; Spasić, S. Associations of oxidative stress status parameters with traditional cardiovascular disease risk factors in patients with schizophrenia. Scand. J. Clin. Lab. Investig. 2014, 74, 184–191.
24. Fukushima, T.; Iizuka, H.; Yokota, A.; Suzuki, T.; Ohno, C.; Kono, Y.; Nishikiori, M.; Seki, A.; Ichiba, H.; Watanabe, Y.; et al. Quantitative analyses of schizophrenia-associated metabolites in serum: Serum D-lactate levels are negatively correlated with gamma-glutamylcysteine in medicated schizophrenia patients. PLoS ONE 2014, 9, e101652.
25. Gonzalez-Liencres, C.; Tas, C.; Brown, E.C.; Erdin, S.; Onur, E.; Cubukcoglu, Z.; Aydemir, O.; Esen-Danaci, A.; Brüne, M. Oxidative stress in schizophrenia: A case-control study on the effects on social cognition and neurocognition. BMC Psychiatry 2014, 14, 268.
26. Tsai, M.C.; Liou, C.W.; Lin, T.K.; Lin, I.M.; Huang, T.L. Changes in oxidative stress markers in patients with schizophrenia: The effect of antipsychotic drugs. Psychiatry Res. 2013, 209, 284–290.
27. Tao, Q.; Miao, Y.; Li, H.; Yuan, X.; Huang, X.; Wang, Y.; Andreassen, O.A.; Fan, X.; Yang, Y.; Song, X. Insulin Resistance and Oxidative Stress: In Relation to Cognitive Function and Psychopathology in Drug-Naïve, First-Episode Drug-Free Schizophrenia. Front. Psychiatry 2020, 11, 537280.
28. Cruz, B.F.; de Campos-Carli, S.M.; de Oliveira, A.M.; de Brito, C.B.; Garcia, Z.M.; do Nascimento Arifa, R.D.; de Souza, D.D.G.; Teixeira, A.L.; Salgado, J.V. Investigating potential associations between neurocognition/social cognition and oxidative stress in schizophrenia. Psychiatry Res. 2021, 298, 113832.

29. Raffa, M.; Atig, F.; Mhalla, A.; Kerkeni, A.; Mechri, A. Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients. BMC Psychiatry 2011, 11, 124.

30. Altuntas, I.; Aksoy, H.; Coskun, I.; Cayköylü, A.; Akçay, F. Erythrocyte superoxide dismutase and glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels in schizophrenic patients. Clin. Chem. Lab. Med. 2000, 38, 1277–1281.

31. Pavlović, D. Oxidative stress as marker of positive symptoms in schizophrenia. Facta Univ. 2002, 9, 157–161.

32. Lavoie, S.; Berger, M.; Schlögelhofer, M.; Schäfer, M.R.; Rice, S.; Kim, S.W.; Hesse, J.; McGorry, P.D.; Smesny, S.; Amminger, G.P. Erythrocyte glutathione levels as long-term predictor of transition to psychosis. Transl. Psychiatry 2017, 7, e1064.

33. Yao, J.K.; Leonard, S.; Reddy, R. Altered glutathione redox state in schizophrenia. Dis. Markers 2006, 22, 83–93.

34. Samuelsson, M.; Skogh, E.; Lundberg, K.; Vrethem, M.; Öllinger, K. Taurine and glutathione in plasma and cerebrospinal fluid in olanzapine treated patients with schizophrenia. Psychiatry Res. 2013, 210, 819–824.

35. Jones, D.P.; Carlson, J.L.; Samiec, P.S.; Sternberg, P., Jr.; Mody, V.C., Jr.; Reed, R.L.; Brown, L.A. Glutathione measurement in human plasma. Evaluation of sample collection, storage and derivatization conditions for analysis of dansyl derivatives by HPLC. Clin. Chim. Acta 1998, 275, 175–184.

36. Mills, B.J.; Lang, C.A. Differential distribution of free and bound glutathione and cyst(e)ine in human blood. Biochem. Pharmacol. 1996, 52, 401–406.

37. Wang, A.M.; Pradhan, S.; Coughlin, J.M.; Trivedi, A.; DuBois, S.L.; Crawford, J.L.; Sedlak, T.W.; Nucifora, F.C., Jr.; Nestadt, G.; Nucifora, L.G.; et al. Assessing Brain Metabolism With 7-T Proton Magnetic Resonance Spectroscopy in Patients With First-Episode Psychosis. JAMA Psychiatry 2019, 76, 314–323.

38. Mahadik, S.P.; Mukherjee, S.; Scheffer, R.; Correnti, E.E.; Mahadik, J.S. Elevated plasma lipid peroxides at the onset of nonaffective psychosis. Biol. Psychiatry 1998, 43, 674–679.

39. Pazvantoglu, O.; Selek, S.; Okay, I.T.; Sengul, C.; Karabekiroglu, K.; Dilbaz, N.; Erel, O. Oxidative mechanisms in schizophrenia and their relationship with illness subtype and symptom profile. Psychiatry Clin. Neurosci. 2009, 63, 693–700.

40. Martínez-Cengotitabengoa, M.; Mac-Dowell, K.S.; Leza, J.C.; Micó, J.A.; Fernandez, M.; Echevarría, E.; Sanjuan, J.; Elorza, J.; González-Pinto, A. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. Schizophr. Res. 2012, 137, 66–72.

41. Raffa, M.; Atig, F.; Mhalla, A.; Kerkeni, A.; Mechri, A. Decreased glutathione levels and impaired antioxidant enzyme activities in drug-naive first-episode schizophrenic patients. BMC Psychiatry 2011, 11, 124.

42. Micó, J.A.; Rojas-Corrales, M.O.; Gibert-Rahola, J.; Parellada, M.; Moreno, D.; Fraguas, D.; Graell, M.; Gil, J.; Irazusta, J.; Castro-Fornieles, J.; et al. Reduced antioxidant defense in early onset first-episode psychosis: A case-control study. BMC Psychiatry 2011, 11, 26.

43. Huang, T.T.; Leu, D.; Zou, Y. Oxidative stress and redox regulation on hippocampal-dependent cognitive functions. Arch. Biochem. Biophys. 2015, 576, 2–7.

44. Raffa, M.; Mechri, A.; Othman, L.B.; Fendri, C.; Gaha, L.; Kerkeni, A. Decreased glutathione levels and antioxidant enzyme activities in untreated and treated schizophrenic patients. Prog. Neuropsychopharmacol. Biol. Psychiatry 2009, 33, 1178–1183.

45. Juchnowicz, D.; Dzikowski, M.; Rog, J.; Waszkiewicz, N.; Karakuła, K.H.; Zalewska, A.; Maciejczyk, M.; Karakula-Juchnowicz, H. Pro/Antioxidant State as a Potential Biomarker of Schizophrenia. J. Clin. Med. 2021, 10, 4156.

46. Nucifora, L.G.; Tanaka, T.; Hayes, L.N.; Kim, M.; Lee, B.J.; Matsuda, T.; Nucifora, F.C., Jr.; Sedlak, T.; Mojtabai, R.; Eaton, W.; et al. Reduction of plasma glutathione in psychosis associated with schizophrenia and bipolar disorder in translational psychiatry. Transl. Psychiatry 2017, 7, e1215.

47. Martínez-Cengotitabengoa, M.; Mac-Dowell, K.S.; Leza, J.C.; Micó, J.A.; Fernandez, M.; Echevarría, E.; Sanjuan, J.; Elorza, J.; González-Pinto, A. Cognitive impairment is related to oxidative stress and chemokine levels in first psychotic episodes. Schizophr. Res. 2012, 137, 66–72.

48. Ballesteros, A.; Jiang, P.; Summerfelt, A.; Du, X.; Chiappelli, J.; O'Donnell, P.; Kochunov, P.; Hong, L.E. No evidence of exogenous origin for the abnormal glutathione redox state in schizophrenia. Schizophr. Res. 2013, 146, 184–189.

49. Ballesteros, A.; Summerfelt, A.; Du, X.; Jiang, P.; Chiappelli, J.; Tagamets, M.; O'Donnell, P.; Kochunov, P.; Hong, L.E. Electrophysiological intermediate biomarkers for oxidative stress in schizophrenia. Clin. Neurophysiol. 2013, 124, 2209–2215.

50. Matsuzawa, D.; Obata, T.; Shirayama, Y.; Nonaka, H.; Kanazawa, Y.; Yoshitome, E.; Takanashi, J.; Matsuda, T.; Shimizu, E.; Ikehira, H.; et al. Negative correlation between brain glutathione level and negative symptoms in schizophrenia: A 3T 1H-MRS study. PLoS ONE 2008, 3, e1944.

51. Tsugawa, S.; Noda, Y.; Tarumi, R.; Mimura, Y.; Yoshida, K.; Iwata, Y.; Elsalhy, M.; Kuromiya, M.; Kurose, S.; Masuda, F.; et al. Glutathione levels and activities of glutathione metabolism enzymes in patients with schizophrenia: A systematic review and meta-analysis. J. Psychopharmacol. 2019, 33, 1199–1214.

52. Altuntas, I.; Aksoy, H.; Coskun, I.; Cayköylü, A.; Akçay, F. Erythrocyte superoxide dismutase and glutathione peroxidase activities, and malondialdehyde and reduced glutathione levels in schizophrenic patients. Clin. Chem. Lab. Med. 2000, 38, 1277–1281.

53. Dadheech, G.; Sharma, P.; Gautam, S. Oxidative Stress-Induced Response of Some Endogenous Antioxidants in Schizophrenia. Indian J. Clin. Biochem. 2012, 27, 278–283.

54. Martínez-Cengotitabengoa, M.; Micó, J.A.; Arango, C.; Castro-Fornieles, J.; Graell, M.; Payá, B.; Leza, J.C.; Zorrilla, I.; Parellada, M.; López, M.P.; et al. Basal low antioxidant capacity correlates with cognitive deficits in early onset psychosis. A 2-year follow-up study. Schizophr. Res. 2014, 156, 23–29.

55. Wood, S.J.; Berger, G.E.; Wellard, R.M.; Proffitt, T.M.; McConchie, M.; Berk, M.; McGorry, P.D.; Pantelis, C. Medial temporal lobe glutathione concentration in first episode psychosis: A 1H-MRS investigation. Neurobiol. Dis. 2009, 33, 354–357.

56. Do, K.Q.; Trabesinger, A.H.; Kirsten-Krüger, M.; Lauer, C.J.; Dydak, U.; Hell, D.; Holsboer, F.; Boesiger, P.; Cuénod, M. Schizophrenia: Glutathione deficit in cerebrospinal fluid and prefrontal cortex in vivo. Eur. J. Neurosci. 2000, 12, 3721–3728.

57. Reyes-Madrigal, F.; León-Ortiz, P.; Mao, X.; Mora-Durán, R.; Shungu, D.C.; de la Fuente-Sandoval, C. Striatal Glutathione in First-episode Psychosis Patients Measured In Vivo with Proton Magnetic Resonance Spectroscopy. Arch. Med. Res. 2019, 50, 207–213.

58. Das, T.K.; Javadzadeh, A.; Dey, A.; Sabesan, P.; Théberge, J.; Radua, J.; Palaniyappan, L. Antioxidant defense in schizophrenia and bipolar disorder: A meta-analysis of MRS studies of anterior cingulate glutathione. Prog. Neuropsychopharmacol. Biol. Psychiatry 2019, 91, 94–102.

59. Kumar, J.; Liddle, E.B.; Fernandes, C.C.; Palaniyappan, L.; Hall, E.L.; Robson, S.E.; Simmonite, M.; Fiesal, J.; Katshu, M.Z.; Qureshi, A.; et al. Glutathione and glutamate in schizophrenia: A 7T MRS study. Mol. Psychiatry 2020, 25, 873–882.

60. Rae, C.D.; Williams, S.R. Glutathione in the human brain: Review of its roles and measurement by magnetic resonance spectroscopy. Anal. Biochem. 2017, 529, 127–143.

61. Palaniyappan, L.; Park, M.T.M.; Jeon, P.; Limongi, R.; Yang, K.; Sawa, A.; Théberge, J. Is There a Glutathione Centered Redox Dysregulation Subtype of Schizophrenia? Antioxidants 2021, 10, 1703.

62. Smaga, I.; Frankowska, M.; Filip, M. N-acetylcysteine as a new prominent approach for treating psychiatric disorders. Br. J. Pharmacol. 2021, 178, 2569–2594.

63. Samuni, Y.; Goldstein, S.; Dean, O.M.; Berk, M. The chemistry and biological activities of N- acetylcysteine. Biochim. Biophys. Acta 2013, 1830, 4117–4129.

64. Tardiolo, G.; Bramanti, P.; Mazzon, E. Overview on the Effects of N-Acetylcysteine in Neurodegenerative Diseases. Molecules 2018, 23, 3305.

65. Choy, K.H.; Dean, O.; Berk, M.; Bush, A.I.; van den Buuse, M. Effects of N-acetyl-cysteine treatment on glutathione depletion and a short-term spatial memory deficit in 2-cyclohexene-1-one-treated rats. Eur. J. Pharmacol. 2010, 649, 224–228.

66. Monte, A.S.; da Silva, F.E.R.; Lima, C.N.C.; Vasconcelos, G.S.; Gomes, N.S.; Miyajima, F.; Vasconcelos, S.M.M.; Gama, C.S.; Seeman, M.V.; de Lucena, D.F.; et al. Sex influences in the preventive effects of N-acetylcysteine in a two-hit animal model of schizophrenia. J. Psychopharmacol. 2020, 34, 125–136.

67. Conus, P.; Seidman, L.J.; Fournier, M.; Xin, L.; Cleusix, M.; Baumann, P.S.; Ferrari, C.; Cousins, A.; Alameda, L.; Gholam-Rezaee, M.; et al. N-acetylcysteine in a Double-Blind Randomized Placebo-Controlled Trial: Toward Biomarker-Guided Treatment in Early Psychosis. Schizophr. Bull. 2018, 44, 317–327.

68. Retsa, C.; Knebel, J.F.; Geiser, E.; Ferrari, C.; Jenni, R.; Fournier, M.; Alameda, L.; Baumann, P.S.; Clarke, S.; Conus, P.; et al. Treatment in early psychosis with N-acetyl-cysteine for 6months improves low-level auditory processing: Pilot study. Schizophr. Res. 2018, 191, 80–86.

69. Breier, A.; Liffick, E.; Hummer, T.A.; Vohs, J.L.; Yang, Z.; Mehdiyoun, N.F.; Visco, A.C.; Metzler, E.; Zhang, Y.; Francis, M.M. Effects of 12-month, double-blind N-acetyl cysteine on symptoms, cognition and brain morphology in early phase

schizophrenia spectrum disorders. Schizophr. Res. 2018, 199, 395–402.

70. Berk, M.; Copolov, D.; Dean, O.; Lu, K.; Jeavons, S.; Schapkaitz, I.; Anderson-Hunt, M.; Judd, F.; Katz, F.; Katz, P.; et al. N-acetyl cysteine as a glutathione precursor for schizophrenia--a double-blind, randomized, placebo-controlled trial. Biol. Psychiatry 2008, 64, 361–368.
71. Sepehrmanesh, Z.; Heidary, M.; Akasheh, N.; Akbari, H.; Heidary, M. Therapeutic effect of adjunctive N-acetyl cysteine (NAC) on symptoms of chronic schizophrenia: A double-blind, randomized clinical trial. Prog. Neuropsychopharmacol. Biol. Psychiatry 2018, 82, 289–296.
72. Rapado-Castro, M.; Dodd, S.; Bush, A.I.; Malhi, G.S.; Skvarc, D.R.; On, Z.X.; Berk, M.; Dean, O.M. Cognitive effects of adjunctive N-acetyl cysteine in psychosis. Psychol. Med. 2017, 47, 866–876.
73. Farokhnia, M.; Azarkolah, A.; Adinehfar, F.; Khodaie-Ardakani, M.R.; Hosseini, S.M.; Yekehtaz, H.; Tabrizi, M.; Rezaei, F.; Salehi, B.; Sadeghi, S.M.; et al. N-acetylcysteine as an adjunct to risperidone for treatment of negative symptoms in patients with chronic schizophrenia: A randomized, double-blind, placebo-controlled study. Clin. Neuropharmacol. 2013, 36, 185–192.
74. Yolland, C.O.; Hanratty, D.; Neill, E.; Rossell, S.L.; Berk, M.; Dean, O.M.; Castle, D.J.; Tan, E.J.; Phillipou, A.; Harris, A.W.; et al. Meta-analysis of randomised controlled trials with N-acetylcysteine in the treatment of schizophrenia. Aust. N. Z. J. Psychiatry 2020, 54, 453–466.
75. Mullier, E.; Roine, T.; Griffa, A.; Xin, L.; Baumann, P.S.; Klauser, P.; Cleusix, M.; Jenni, R.; Alemàn-Gómez, Y.; Gruetter, R.; et al. N-Acetyl-Cysteine Supplementation Improves Functional Connectivity Within the Cingulate Cortex in Early Psychosis: A Pilot Study. Int. J. Neuropsychopharmacol. 2019, 22, 478–487.
76. Klauser, P.; Xin, L.; Fournier, M.; Griffa, A.; Cleusix, M.; Jenni, R.; Cuenod, M.; Gruetter, R.; Hagmann, P.; Conus, P.; et al. N-acetylcysteine add-on treatment leads to an improvement of fornix white matter integrity in early psychosis: A double-blind randomized placebo-controlled trial. Transl. Psychiatry 2018, 8, 220.
77. Hardingham, G.E.; Do, K.Q. Linking early-life NMDAR hypofunction and oxidative stress in schizophrenia pathogenesis. Nat. Rev. Neurosci. 2016, 17, 125–134.
78. Steullet, P.; Neijt, H.C.; Cuénod, M.; Do, K.Q. Synaptic plasticity impairment and hypofunction of NMDA receptors induced by glutathione deficit: Relevance to schizophrenia. Neuroscience 2006, 137, 807–819.
79. Lipton, S.A.; Choi, Y.B.; Takahashi, H.; Zhang, D.; Li, W.; Godzik, A.; Bankston, L.A. Cysteine regulation of protein function--as exemplified by NMDA-receptor modulation. Trends Neurosci. 2002, 25, 474–480.
80. Köhr, G.; Eckardt, S.; Lüddens, H.; Monyer, H.; Seeburg, P.H. NMDA receptor channels: Subunit-specific potentiation by reducing agents. Neuron 1994, 12, 1031–1040.
81. Do, K.Q.; Cabungcal, J.H.; Frank, A.; Steullet, P.; Cuenod, M. Redox dysregulation, neurodevelopment, and schizophrenia. Curr. Opin. Neurobiol. 2009, 19, 220–230.
82. Zhuo, D.Y.; Wu, Y.L.; Yao, W.X.; Cao, Y.; Wu, C.F.; Tanaka, M. Effect of MK-801 and ketamine on hydroxyl radical generation in the posterior cingulate and retrosplenial cortex of free-moving mice, as determined by in vivo microdialysis. Pharmacol. Biochem. Behav. 2007, 86, 1–7.
83. Radonjić, N.V.; Knezević, I.D.; Vilimanovich, U.; Kravić-Stevović, T.; Marina, L.V.; Nikolić, T.; Todorović, V.; Bumbasirević, V.; Petronijević, N.D. Decreased glutathione levels and altered antioxidant defense in an animal model of schizophrenia: Long-term effects of perinatal phencyclidine administration. Neuropharmacology 2010, 58, 739–745.
84. Da Silva, F.C.; do Carmo de Oliveira Cito, M.; da Silva, M.I.; Moura, B.A.; de Aquino Neto, M.R.; Feitosa, M.L.; de Castro Chaves, R.; Macedo, D.S.; de Vasconcelos, S.M.; de França Fonteles, M.M.; et al. Behavioral alterations and pro-oxidant effect of a single ketamine administration to mice. Brain Res. Bull. 2010, 83, 9–15.
85. Baxter, P.S.; Bell, K.F.; Hasel, P.; Kaindl, A.M.; Fricker, M.; Thomson, D.; Cregan, S.P.; Gillingwater, T.H.; Hardingham, G.E. Synaptic NMDA receptor activity is coupled to the transcriptional control of the glutathione system. Nat. Commun. 2015, 6, 6761, Erratum in Nat. Commun. 2017, 8, 16158.
86. Back, S.A.; Gan, X.; Li, Y.; Rosenberg, P.A.; Volpe, J.J. Maturation-dependent vulnerability of oligodendrocytes to oxidative stress-induced death caused by glutathione depletion. J. Neurosci. 1998, 18, 6241–6253.
87. Smith, J.; Ladi, E.; Mayer-Proschel, M.; Noble, M. Redox state is a central modulator of the balance between self-renewal and differentiation in a dividing glial precursor cell. Proc. Natl. Acad. Sci. USA 2000, 97, 10032–10037.
88. Kannan, R.; Kuhlenkamp, J.F.; Jeandidier, E.; Trinh, H.; Ookhtens, M.; Kaplowitz, N. Evidence for carrier-mediated transport of glutathione across the blood-brain barrier in the rat. J. Clin. Investig. 1990, 85, 2009–2013.