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Treatment-resistant schizophrenia: focus on the transsulfuration pathway

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Abstract: Treatment-resistant schizophrenia (TRS) is a severe form of schizophrenia. The severity of illness is positively related to homocysteine levels, with high homocysteine levels due to the low activity of the transsulfuration pathway, which metabolizes homocysteine in synthesizing L-cysteine. Glutathione levels are low in schizophrenia, which indicates shortages of L-cysteine and low activity of the transsulfuration pathway. Hydrogen sulfide (H_2S) levels are low in schizophrenia. H_2S is synthesized by cystathionine β-synthase and cystathionine γ-lyase, which are the two enzymes in the transsulfuration pathway. Iron-sulfur proteins obtain sulfur from L-cysteine. The oxidative phosphorylation (OXPHOS) pathway has various iron-sulfur proteins. With low levels of L-cysteine, iron-sulfur cluster formation will be dysregulated leading to deficits in OXPHOS in schizophrenia. Molybdenum cofactor (MoCo) synthesis requires sulfur, which is obtained from L-cysteine. With low levels of MoCo synthesis, molybdenum-dependent sulfite oxidase (SUOX) will not be synthesized at appropriate levels. SUOX detoxifies sulfite from sulfur-containing amino acids. If sulfites are not detoxified, there can be sulfite toxicity. The transsulfuration pathway metabolizes selenomethionine, whereby selenium from selenomethionine can be used for selenoprotein synthesis. The low activity of the transsulfuration pathway decreases selenoprotein synthesis. Glutathione peroxidase (GPX), with various GPXs being selenoprotein, is low in schizophrenia. The dysregulations of selenoproteins would lead to oxidant stress, which would increase the methylation of genes and histones leading to epigenetic changes in TRS. An add-on treatment to mainline antipsychotics is proposed for TRS that targets the dysregulations of the transsulfuration pathway and the dysregulations of other pathways stemming from the transsulfuration pathway being dysregulated.

Keywords: cystathionine β-synthase; cystathionine γ-lyase; glutathione peroxidase; homocysteine; iron-sulfur cluster; oxidative phosphorylation; sulfite oxidase; treatment-resistant schizophrenia.

Introduction

Almost 60% of patients with schizophrenia fail to effectively respond to antipsychotics after 23 weeks of treatment, with treatment costs that are 3–11 times higher for patients with treatment-resistant schizophrenia (TRS; Kennedy et al., 2014). When TRS is defined as a lack of effectiveness after two adequate trials of antipsychotics, 30% of individuals with schizophrenia are treatment resistant (Meltzer, 1997). TRS can lead to severe, lifelong difficulties for individuals with TRS. Due to the lack of control of symptoms of schizophrenia, individuals with TRS can end up in prisons as long-term patients at mental hospitals or homeless. The probability of individuals with schizophrenia becoming homeless is positively related to the severity of their illness (Olfson et al., 1999). In Los Angeles, 13.7% of individuals who were in homeless shelters had schizophrenia (Koegel et al., 1988). Clozapine is considered the gold standard in the treatment of TRS (Souza et al., 2013). Clozapine, however, can have severe side effects, such as sedation (70%), hypersalivation (57%), sexual side effects (55%), loss of energy (42%), nocturnal enuresis (39%), memory problems (38%), lack of concentration (38%), headache (35%), constipation (34%), dysphoria (32%), weight gain (31%), tachycardia (30%), postural hypotension (27%), nausea/vomiting (24%), blurred vision (24%), and increased sweating (21%; Yusufi et al., 2007). Clozapine has five black-box warnings for agranulocytosis, seizures, myocarditis, other adverse cardiovascular, and respiratory effects and increased mortality in elderly patients with dementia-related psychoses. There is some debate as to whether clozapine is more effective than other antipsychotics in the treatment of TRS. One meta-analysis points to clozapine as being no

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more effective in the treatment of TRS than other antipsychotics (Samara et al., 2016). Furthermore, treatment with clozapine demands constant monitoring, which can be costly.

This paper holds that TRS is due to pronouncedly low activity in the transsulfuration pathway, which leads to other pathways also being dysregulated. Homocysteine levels could be high in schizophrenia due to homocysteine not being remethylated to L-methionine (Moustafa et al., 2014) or due to the low activity of the transsulfuration pathway, which in synthesizing L-cysteine metabolizes homocysteine. The paper presents evidence that the activity of the transsulfuration pathway is low in schizophrenia, which leads to the high homocysteine levels seen in schizophrenia.

The transsulfuration pathway synthesizes L-cysteine from homocysteine (see Figure 1). With the decreased activity of the transsulfuration pathway, homocysteine levels will increase as cystathionine β-synthase (CBS), the first enzyme in the transsulfuration pathway, metabolizes homocysteine. Research shows that homocysteine levels are increased in schizophrenia. Plasma homocysteine levels are increased in young male patients with schizophrenia who were medicated compared to controls (Levine et al., 2002). Plasma homocysteine levels are increased in both male and female patients with schizophrenia who were medicated compared to controls (Haidemenos et al., 2007). Serum homocysteine levels are increased in patients with schizophrenia who were medicated compared to controls (Eren et al., 2010). There are increased homocysteine levels in red blood cells in patients with schizophrenia who had never been medicated compared to controls (Kale et al., 2010). Serum homocysteine levels in first-episode unmedicated schizophrenia are increased compared to controls (Liu et al., 2019). A meta-analysis indicated that a 5 μm/l increase in plasma homocysteine levels is associated with a 70% increase in the risk of developing schizophrenia (Muntjewerff et al., 2006). There is a 2.15 odds ratio (95% confidence interval = 1.39–3.32; $p = 5.3 \times 10^{-4}$) increase in risk schizophrenia for every 1 standard deviation increase in the natural log-transformed plasma total homocysteine levels (Numata et al., 2015).

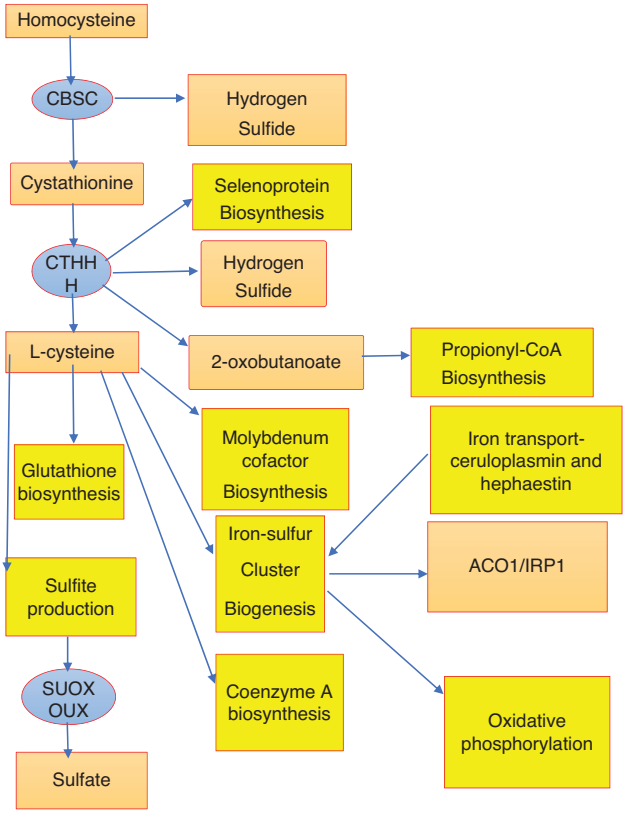

Figure 1: Transsulfuration pathway (CBS and CTH) and downstream pathways.

The severity of symptoms in schizophrenia is positively associated with higher levels of homocysteine. Negative symptoms are positively correlated with plasma levels of homocysteine in patients who were medicated (Petronijević et al., 2008). In patients with schizophrenia who were unmedicated, plasma levels of homocysteine are positively correlated with negative symptoms (Bouaziz et al., 2010). Plasma homocysteine levels are positively correlated with negative symptoms (Misiak et al., 2014). A review article (Moustafa et al., 2014) indicated that negative symptoms of schizophrenia are positively correlated with homocysteine levels. Plasma homocysteine levels are positively correlated with depression in schizophrenia (Narayan et al., 2014). As TRS is defined as the lack of effectiveness after two adequate antipsychotic trials, individuals with TRS are severely ill.

We also detail how targeting dysregulations of the transsulfuration pathway and dysregulations of other pathways that stem from dysregulations of the transsulfuration pathway, via an add-on treatment to mainline antipsychotics, could be an effective treatment for TRS, where (a) levels of molybdenum-containing proteins are increased through supplementation with sodium molybdate; (b) levels of selenoproteins are increased through supplementation with Se-methylselenocysteine; (c) the activity of enzymes in the transsulfuration pathway is increased through supplementation with taurine, L-arginine, and L-citrulline; (d) iron-sulfur proteins involved in oxidative phosphorylation (OXPHOS) are increased through supplementation with iron from iron sulfate, coenzyme Q10, copper, pantothenic acid, and acetyl-L-carnitine; (e) enzymes involved in L-cysteine metabolism and selenium metabolism are supported by

vitamin B6; and (f) increased protein synthesis is supported by supplementation with whey protein. All three dimensions of schizophrenia, positive symptoms, negative symptoms, and symptoms of disorganization, would be treated by the proposed treatment.

The proposed treatment would obviate the need for patients to take clozapine, whereby patients would avoid all side effects of clozapine and could allow reductions in dosages of mainline antipsychotics. This paper focuses on TRS and the transsulfuration pathway on two grounds. First, TRS is a severe form of illness where the severity of illness is positively associated with homocysteine levels. Research indicates that increased homocysteine levels in schizophrenia are due to the low activity of the transsulfuration pathway. Second, there is a great need for more treatment options for TRS. In terms of translational medicine, TRS has a high priority. TRS is not a subtype of schizophrenia but only schizophrenia that is severe, which is marked by pronouncedly high homocysteine levels. The proposed treatment could generally be effective in the treatment of schizophrenia.

Further evidence of the dysregulations of the transsulfuration pathway and L-cysteine metabolism in schizophrenia

L-cysteine is a rate-limiting factor in the synthesis of glutathione, which is a tripeptide that consists of L-cysteine, L-glutamic acid, and glycine (Lu, 2013). With low levels of L-cysteine synthesized due to the low activity of the transsulfuration pathway, glutathione levels will be decreased. The levels of glutathione in the cerebrospinal fluid and prefrontal cortex *in vivo* are decreased compared to controls in patients with schizophrenia who were drug free (Do et al., 2000). Glutathione levels are inversely correlated, as shown by proton magnetic resonance spectroscopy, with negative symptoms in medicated patients (Matsuzawa et al., 2008). Glutathione levels are decreased in blood of both medicated and unmedicated patients with schizophrenia compared to controls (Raffa et al., 2009). Blood levels of glutathione are decreased in drug-naïve first episode patients with schizophrenia compared to controls (Raffa et al., 2011) Glutathione levels are decreased in plasma of patients with schizophrenia who were medicated compared to controls (Nucifora et al., 2017).

Hydrogen sulfide (H_2S) is synthesized by CBS and cystathionine γ-lyase (CTH; Kimura, 2011), which are the two enzymes in the transsulfuration pathway. H_2S is critical to brain function (Paul and Snyder, 2017). H_2S levels are decreased in plasma of individuals with schizophrenia and are negatively correlated to disease severity (Xiong et al., 2018). Decreased levels of H_2S in schizophrenia indicate that enzymes in the transsulfuration pathway are underactive in schizophrenia. The actions of H_2S and nitric oxide are closely related (Altaany et al., 2013). Disrupting H_2S synthesis would adversely affect the physiological actions of nitric oxide, which would worsen schizophrenia symptoms.

Plants synthesize selenomethionine, with 90% of selenium in plants in the form of selenomethionine, which in humans when ingested is converted to selenide via the transsulfuration pathway with the selenium then able to be used for selenoprotein synthesis (Burk and Hill, 2015). Glutathione peroxidases (GPX), with GPX1 to GPX4 and GPX6 being selenoproteins, neutralize hydrogen peroxide (H_2O_2; Brigelius-Flohé and Maiorino, 2013). A meta-analysis indicated that GPX levels are low in schizophrenia (Tsugawa et al., 2019). A 67% suppression of GPX is observed in blood platelets in patients with schizophrenia (Dietrich-Muszalska and Kwiatkowska, 2014).

The expression of mRNA of the two subunits of the cystine/glutamate antiporter system xc^-, solute carrier 3A2 (SLC3A2) and solute carrier 7A11 (SLC7A11), is decreased in white blood cells in schizophrenia (Lin et al., 2016). The cystine/glutamate antiporter transports cystine into cells and glutamate out of cells (Bridges et al., 2012). Cystine transported into cells is reduced to L-cysteine. In schizophrenia, L-cysteine levels in cells could be low due to the low levels of SLC3A2 and SLC7A11. Iron regulates glutamate secretion via aconitase 1 (ACO1; McGahan et al., 2005), with ACO1 doing so by ACO1 increasing transport by the cystine/glutamate antiporter (Lall et al., 2008). Levels of SLC3A2 and SLC7A11 could be low in schizophrenia due to decreased iron-sulfur cluster formation. ACO1 converts to iron regulatory protein 1 (IRP1) upon the loss of a 4Fe-4S iron-sulfur cluster (Dupuy et al., 2006), upon which ACO1 is not available to increase the activity of the cystine-glutamate antiporter. Cysteine desulfurase is required for the reformation of a 4Fe-4S iron-sulfur cluster on IRP1 (Li et al., 2006). The cystine/glutamate antiporter releases glutamate into synapses, thereby increasing glutaminergic neurotransmission (Massie et al., 2015). Down-regulation of the cystine/glutamate antiporter in schizophrenia would decrease glutaminergic neurotransmission in schizophrenia (Lin et al., 2016). Serum levels of L-cysteine could be misleading, as with

the cystine/glutamate antiporter dysregulated there could be high levels of serum L-cysteine, whereas there are low levels of L-cysteine in cells due to cystine not being transported into cells.

IRP1 destabilizes the mRNA transcripts of hypoxia-inducible factor 2α (HIF2α; Anderson et al., 2013). With high levels of IRP1 due to decreased iron-sulfur cluster formation, HIF2α mRNAs will be degraded. The transcription of the gene for CBS is induced by HIFs (Takano et al., 2014). With low levels of HIF2α due to high levels of IRP1, the transcription of the gene for CBS will be low and homocysteine levels will be high. High homocysteine levels seen in schizophrenia could lead to the hypermethylation of the gene for CTH. Hyperhomocysteinemia is associated with increased DNA methyltransferases and DNA hypermethylation of CTH (Li et al., 2015).

Sulfite oxidase and L-cysteine metabolism

Sulfites from L-cysteine and L-methionine metabolism must be detoxified, which is accomplished by sulfite oxidase (SUOX) that synthesizes sulfate from sulfite. SUOX deficiency is a life-threatening illness where there is severe neurological impairment for which there is no effective treatment (Claerhout et al., 2018). A genome-wide study of schizophrenia with 36,989 cases did not associate the gene for SUOX with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). No genetic difficulties in schizophrenia with the gene for SUOX are being postulated by this paper.

The molybdenum cofactor (MoCo) consists of molybdenum bound to molybdopterin (Mendel, 2013). Cysteine desulfurase by transferring sulfur from L-cysteine to MoCo synthesis 3 (MOCS3) provides sulfur required for MoCo biosynthesis in humans (Marelja et al., 2008, 2013). L-cysteine via cysteine desulfurase supplies sulfur for both MoCo and iron-sulfur cluster formation. Genetic loci near the genetic location for cysteine desulfurase are not associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Genetic loci near the genetic location of MOCS3 are not associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

What is being proposed by this paper is at the stage where cysteine desulfurase transfers sulfur from L-cysteine to MOCS3, due to shortages of L-cysteine, which MOCS3 does not obtain the needed sulfur whereby there will be low levels of MoCo and molybdenum-containing proteins, such as SUOX. CTH, which synthesizes L-cysteine, is highly expressed in the liver (Fagerberg et al., 2014). With CTH underactive in the liver, L-cysteine will not be appropriately synthesized in the liver, whereby the synthesis of molybdenum-containing proteins could systematically be adversely affected in schizophrenia. Low serum levels of molybdenum are found in patients with schizophrenia compared to healthy controls (Cao et al., 2019), which increases the difficulties in schizophrenia in synthesizing SUOX.

Xanthine oxidase (XO) is a molybdenum-containing protein (Ryan et al., 1995). XO is decreased in the occipital cortex and thalamus of patients with schizophrenia (Michel et al., 2011). Uric acid is synthesized by XO. Inhibitors of XO, such as allopurinol, are used to lower uric acid levels in the treatment of gout. Plasma uric acid levels are significantly decreased in schizophrenia in both medicated and unmedicated patients compared to controls and inversely related to psychosis (Yao et al., 1998). Research shows that plasma uric acid levels are significantly lower in first-episode patients with schizophrenia compared to controls (Reddy et al., 2003; Yao et al., 2010). Given the low levels of molybdopterin in schizophrenia, the synthesis of SUOX would also be adversely affected in schizophrenia. This paper proposes that there can be difficulties in synthesizing molybdopterin and molybdenum-containing proteins due to shortages of L-cysteine leading to decreases in the synthesis of SUOX.

Sulfites are held to be toxic in babies born with mutated SUOX genes, as sulfites adversely affect glutamatergic neurotransmission and inhibit glutathione metabolism-related enzymes in the cortex (Parmeggiani et al., 2015). Sulfites inhibit glutamate dehydrogenase and inhibit 2-oxoglutarate synthesis (Zhang et al., 2004). Sulfites adversely affect NMDA receptors by degrading the NR2A and NR2B subunits of the NMDA receptor (Oztürk et al., 2006). Dysregulation of glutamatergic neurotransmission has been hypothesized as leading to the development of schizophrenia (Uno and Coyle, 2019). High levels of sulfites in schizophrenia due to decreases in SUOX due to decreases in L-cysteine synthesis would lead to the dysregulations of glutamatergic neurotransmission in schizophrenia.

OXPHOS in schizophrenia

L-cysteine via cysteine desulfurase supplies sulfur for iron-sulfur cluster formation (Li et al., 2006). Due

to the low activity of the transsulfuration pathway in schizophrenia, there will not be sufficient L-cysteine for iron-sulfur cluster formation, which will dysregulate iron-sulfur proteins leading to deficits in OXPHOS. OXPHOS is highly dependent on proteins with iron-sulfur clusters. NADH dehydrogenase, the first enzyme in the OXPHOS pathway, contains up to 10 proteins with iron-sulfur clusters depending on species (Gnandt et al., 2016). Succinate dehydrogenase, an enzyme in the OXPHOS pathway, contains three iron-sulfur clusters (Johnson et al., 1985). Ubiquinol-cytochrome *c* reductase, an enzyme in the OXPHOS pathway, contains iron-sulfur clusters (1998). Electron transfer flavoprotein dehydrogenase, an enzyme that contributes to OXPHOS, also contains iron-sulfur clusters (Watmough and Frerman, 2010).

Research shows that there are dysfunctions in OXPHOS in schizophrenia. In postmortem brains of individuals who had schizophrenia, there is a decrease in cytochrome *c* oxidase activity of 63% in the nucleus caudatus ($p < 0.0001$) and a 43% reduction in the cortex gyrus frontalis ($p < 0.05$) compared to controls (Cavelier et al., 1995). There is a significant decrease in the activity complex I in peripheral blood mononuclear cells of individuals with schizophrenia who were medicated compared to controls (Gubert et al., 2013). Research from imaging, transcriptomic, proteomic, and metabolomic studies points to there being deficits in OXPHOS in schizophrenia (Bergman and Ben-Shachar, 2016). A review indicated that there are multifaceted mitochondrial deficits in schizophrenia in complex I of the OXPHOS pathway (Ben-Shachar, 2017). There is a down-regulation of nuclear mRNA molecules and proteins involved in OXPHOS and decreases in high energy phosphates in brains in schizophrenia (Clay et al., 2011). In postmortem brains of individuals who had schizophrenia, complex IV is significantly reduced in the frontal cortex and temporal cortex and the activity of complexes I + III is significantly reduced in the temporal cortex and basal ganglia compared to healthy controls (Maurer et al., 2001). Deficits in OXPHOS would decrease ATP levels as the OXPHOS pathway synthesizes ATP. There are ATP decreases in the frontal lobes of individuals with schizophrenia who were predominantly unmedicated compared to controls (Volz et al., 2000). Medication status could affect test results on high energy phosphates in schizophrenia (Jayakumar et al., 2010).

This paper proposes that although there are dysregulations in OXPHOS in schizophrenia there is also oxidant stress in schizophrenia due to the dysregulations of selenium-dependent GPXs, which neutralize H_2O_2 and also due to decreased levels of glutathione in schizophrenia. Research indicates that there is a significant down-regulation of the OXPHOS pathway in schizophrenia and that down-regulation of the OXPHOS pathway is associated with oxidant stress (Prabakaran et al., 2004). A significant decrease in complex I activity in peripheral blood mononuclear cells has been observed in patients with schizophrenia compared to controls, whereas at the same time there is an increase in plasma thiobarbituric acid-reactive substances in patients with schizophrenia compared to matched controls (Gubert et al., 2013). Deficits in OXPHOS and oxidant stress are not mutually exclusive outcomes in schizophrenia. A major point of this paper is that there is oxidant stress in schizophrenia and that such oxidant stress is due to the dysregulations of GPXs and dysregulations of glutathione synthesis. As discussed below, oxidant stress can dysregulate epigenetic mechanisms in schizophrenia.

A proposal for how dysregulations of the transsulfuration pathway could affect the symptoms of schizophrenia

High levels of sulfites in schizophrenia could lead to dysregulations of glutamatergic neurotransmission and positive symptoms. Negative symptoms in research on schizophrenia address the behavioral deficits seen in schizophrenia. Negative symptoms are highly prevalent in schizophrenia and are not well addressed by current pharmacological treatments (Buckley and Stahl, 2007; Möller and Czobor, 2015). Many proteins in the OXPHOS pathway are iron-sulfur proteins. Mitochondria via OXPHOS provide most of the energy for animal cells (Saraste, 1999). With deficits in OXPHOS in schizophrenia, there will be energy deficits leading to behavioral deficits in schizophrenia, which are termed the negative symptoms of schizophrenia. Selenoproteins as antioxidants play an important role in the central nervous system function (Steinbrenner and Sies, 2013). Research indicates that the dysregulations of selenoproteins are involved in a range of neurological illnesses (Pillai et al., 2014; Cardoso et al., 2015). The three dimensions of schizophrenia are divided into positive symptoms, negative symptoms, and symptoms of disorganization (Malla et al., 1993). Dysregulation of selenoproteins in schizophrenia could lead to diffuse oxidant stress in the brain, which could lead to symptoms of disorganization that are very frequently seen in schizophrenia.

How schizophrenia differentiates from other illnesses where the transsulfuration pathway is dysregulated

High homocysteine levels have been implicated in various illnesses besides schizophrenia (Moustafa et al., 2015). High homocysteine levels are a strong independent risk factor of cerebrovascular, cardiovascular, and peripheral vascular diseases (McKinley, 2000). Hyperhomocysteinemia is present in Alzheimer's disease and increases as Alzheimer's disease progresses (Farina et al., 2017). Homocysteine levels are positively associated with disease severity in Parkinson's disease (Licking et al., 2017). Autism is associated with increased levels of homocysteine (Ali et al., 2011). Homocysteine levels are increased in mania and euthymia in bipolar disorder (Salagre et al., 2017). Homocysteine can have deleterious effects; however, high homocysteine levels in a wide range of illnesses must largely be proxies for other dysregulated biological processes where such other biological processes must be able to deliver a great deal of biological variability. Differing epigenetic dysregulations differentiate illnesses from each other where there are high homocysteine levels. This paper proposes that epigenetic dysregulations play key roles in illnesses where there are high homocysteine levels.

Fe(II) and α-ketoglutarate-dependent ten-eleven translocation (TET) enzymes demethylate DNA (Rasmussen and Helin, 2016), whereas Fe(II) and α-ketoglutarate-dependent JumonjiC-domain-containing enzymes demethylate lysine residues of histones (Tsukada et al., 2006). Levels of the substrate 2-oxoglutarate and levels of tricarboxylic intermediates regulate TET enzymes (Laukka et al., 2016; Bochtler et al., 2017) and JumonjiC-domain-containing histone demethylases (Tarhonskaya et al., 2017). With decreases in activity of ACO1 in the citric acid cycle, there will be decreases in the synthesis of 2-oxglutarate, whereby TET enzymes and JumonjiC-domain-containing enzymes will be dysregulated, which will lead to epigenetic dysregulations in schizophrenia. With high levels of sulfites, glutamate dehydrogenase is inhibited, which will decrease 2-oxoglutarate synthesis by glutamate dehydrogenase (Zhang et al., 2004) that will decrease the activity of DNA-demethylating TET enzymes and JumonjiC-domain-containing histone demethylases.

The dysregulations of the transsulfuration pathway and selenoprotein synthesis could result in a range of illnesses arising from a range of epigenetic changes. Selenium has a wide range of epigenetic effects (Speckmann and Grune, 2015; Jabłońska and Reszka, 2017). GPX enzymes, which are selenoproteins, neutralize H_2O_2. H_2O_2 inhibits TET enzymes and JumonjiC-domain-containing histone demethylases (Niu et al., 2015). The dysregulations of selenoproteins resulting in increased H_2O_2 levels would dysregulate DNA demethylation processes and histone demethylation processes. Selenium levels in sera of individuals with schizophrenia are low compared to controls (Cai et al., 2015), which could contribute to the dysregulations of selenoproteins in schizophrenia. Serum selenium levels are inversely associated with homocysteine levels (González et al., 2004). High homocysteine levels seen in schizophrenia could be partly due to low selenium levels in schizophrenia.

Proposed treatment for TRS

This section discusses the supplements that can help treat TRS (see Tables 1 and 2). All three dimensions of schizophrenia, positive symptoms, negative symptoms, and symptoms of disorganization, could be treated by the proposed treatment.

Supplementation with sodium molybdate will be of assistance. Research has shown that supplementation with sodium molybdate increases the levels of molybdenum-containing proteins. Supplementation of female rats with sodium molybdate significantly increased the activities of xanthine dehydrogenase/oxidase and SUOX in the liver and xanthine dehydrogenase/oxidase in small intestinal mucosa (Wang et al., 1992). Molybdenum glycinate is avoided as, to our knowledge, no research has investigated whether molybdenum glycinate is effective in increasing the levels of molybdenum-containing proteins. The Institute of Medicine has set the tolerable upper level limit for molybdenum at 2000 μg/day (Institute of Medicine (US) Panel on Micronutrients, 2001).

Supplementation with Se-methylselenocysteine will be of assistance. The transsulfuration pathway by way of which L-cysteine is synthesized also metabolizes L-selenomethionine (Burk and Hill, 2015). The transsulfuration pathway is, however, dysregulated in schizophrenia. Se-methylselenocysteine is a form of selenium whose metabolism does not depend on enzymes in the transsulfuration pathway. Enzymes, for example, kynureninase, which catalyze β-eliminations, can metabolize Se-methylselenocysteine (Rooseboom et al., 2002). A trial of Se-methylselenocysteine of up to 800 μg/day for

Table 1: Research presented to clarify the safety profiles of suggested supplements.

Supplement	Research that addresses the safety of recommended supplements
Sodium molybdate	The Institute of Medicine set the tolerable upper level limit for adult humans at 2000 μg/day (Institute of Medicine (US) Panel on Micronutrients, 2001)
Se-methylselenocysteine	The Institute of Medicine set the tolerable upper level limit for adult humans at 400 μg/day (Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds, 2000)
Taurine	The observed safe level is 3 g/day (Shao and Hathcock, 2008)
L-arginine	The observed safe level is 20 g/day (Shao and Hathcock, 2008)
Iron from iron sulfate	Standard treatment for iron deficiency (Santiago, 2012)
Copper from copper gluconate	The Institute of Medicine set the tolerable upper level limit for adult humans at 10 mg/day (Institute of Medicine (US) Panel on Micronutrients, 2001)
Coenzyme Q10	Well tolerated at dosages as high as 2400 mg/day (Huntington Study Group Pre2CARE Investigators et al., 2010)
Pantothenic acid	No reports of toxicity have been reported with pantothenic acid supplementation, but there is not enough information to set a tolerable upper level limit (Institute of Medicine, 1998)
Acetyl-L-carnitine	3 g/day for 1 year was well tolerated (Thai et al., 1996)
Whey protein	Has been frequently supplemented (Pasiakos et al., 2015). Excessively high proteins intakes should be avoided
Vitamin B6	The Institute of Medicine set the tolerable upper level limit for adults at 100 mg/day (Institute of Medicine, 1998)

Table 2: List of all recommended supplements used to treat schizophrenia and TRS as well as the actions of the supplements and symptoms being targeted by such supplements.

Supplements	Actions	Targeted symptoms
Sodium molybdate	Increases SUOX levels, thereby decreasing sulfite levels and enhancing glutaminergic neurotransmission	Positive symptoms
Se-methylselenocysteine	Increases levels of selenoproteins such as GPX, whereby diffuse oxidant attacks in brains are stopped	Symptoms of disorganization
Taurine	Increases activity of CBS and CTH and increases levels of H_2S	Precondition for other supplements to be effective
L-arginine and L-citrulline	Increases activity of CTH	Precondition for other supplements to be effective
Iron from iron sulfate	Supports iron-sulfur cluster formation and OXPHOS	Negative symptoms
Copper from copper gluconate	Assists with iron transport and supports cytochrome *c* oxidase and OXPHOS	Negative symptoms
Coenzyme Q10	Supports OXPHOS	Negative symptoms
Pantothenic acid	Supports coenzyme A synthesis and iron-sulfur cluster formation	Negative symptoms
Acetyl-L-carnitine	Supports acetyl-coenzyme A synthesis	Negative symptoms
Whey protein	Increases synthesis of propionyl-CoA and 2-oxoglutarate and supports increased protein synthesis	Irritability and fatigue
Vitamin B6	Supports L-cysteine and selenium metabolism	Precondition for other supplements to be effective

84 days showed no toxicity (Marshall et al., 2017). Inorganic forms of selenium are more toxic than organic forms of selenium. Hydrogen selenide is very toxic. Sodium selenite and sodium selenate are more directly converted to hydrogen selenide than is Se-methylselenocysteine. Sodium selenite, sodium selenate, and L-selenomethionine, either yeast based or synthetic, are avoided. Se-methylselenocysteine is thought to have superior anticancer properties to other forms of selenium (Medina et al., 2001). The Institute of Medicine has set the tolerable upper level limit for selenium at 400 μg/day (Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds, 2000).

Supplementation with taurine will be of assistance. Taurine increases the activity of CBS and CTH and increases H_2S levels (Sun et al., 2016). High levels

of taurine are associated with low cardiovascular risks (Yamori et al., 2010). Research points to taurine as the nutritional factor in the longevity of Japanese (Yamori et al., 2009). Research shows that supplemental taurine can ameliorate symptoms of first-episode psychosis (O'Donnell et al., 2016). L-cysteine-containing supplements can be toxic (Baker, 2006). L-cysteine-containing supplements are not supplemented at this time. Neither *N*-acetylcysteine nor lipoic acid is supplemented. N-acetyl-L-cysteine (Whillier et al., 2009) and α-lipoic acid (Han et al., 1997) increase L-cysteine levels by decreasing cystine levels. The cystine/glutamate antiporter transports cystine into cells while transporting glutamate out of cells (Bridges et al., 2012). The cystine/glutamate antiporter is important for both the import of cystine into cells and the export of glutamate out of cells. L-cysteine could have to enter cells as cystine via the cystine/glutamate antiporter. The observed safe level for taurine is 3 g/day (Shao and Hathcock, 2008).

Supplementation with a 1:1 L-arginine and L-citrulline combination will be of assistance. L-arginine increases the expression of CTH (Shi et al., 2006; Yanfei et al., 2006). L-citrulline is a precursor of L-arginine that is not metabolized by intestines and liver as is L-arginine (Romero et al., 2006). An L-arginine and L-citrulline combination will provide L-arginine for both the liver and extrahepatically. The observed safe level for L-arginine is 20 g/day (Shao and Hathcock, 2008).

Supplementation with iron from iron sulfate will be of assistance. Due to difficulties in synthesizing iron-sulfur clusters in schizophrenia, there will be low levels of ACO1 in patients with schizophrenia. ACO1 is an iron-sulfur enzyme early in the citric acid cycle. The activity of aconitase is decreased in brains of schizophrenic patients (Bubber et al., 2011). ACO1 is a special focus as ACO1 interconverts with IRP1 (Klausner and Rouault, 1993). IRP1 is an iron-sulfur protein that regulates overall iron metabolism. IRP1 binds to iron-responsive binding elements of mRNA involved in iron metabolism, affecting the stability of mRNA transcripts. The loss of a 4F-4S iron-sulfur cluster by ACO1 is necessary for ACO1 to covert to IRP1 (Klausner and Rouault, 1993). With increases in iron levels, IRP1 gains a 4Fe-4S iron-sulfur cluster and converts to ACO1 (Haile et al., 1992). Dietary iron regulates IRP levels and aconitase levels (Chen et al., 1997). With supplemental iron, aconitase levels will be increased and IRP1 levels will be decreased, which will result in increases in 2-oxoglutrarate synthesis and decreases in IRP, whereby proteins involved in iron metabolism will be appropriately regulated. Iron sulfate due to good bioavailability, efficacy, and acceptable is the standard treatment for iron deficiency (Santiago, 2012).

Supplementation with copper from copper gluconate will be of assistance. Copper ferroxidases are required for iron transport (Frazer and Anderson, 2014; Jiang et al., 2015, 2016). Copper is also required for the activity of cytochrome *c* oxidase, which is an enzyme is the OXPHOS pathway. Research shows that cytochrome *c* oxidase levels are significantly lower in postmortem brain tissue of individuals who had schizophrenia compared to controls (Cavelier et al., 1995). Copper glycinate is avoided as almost no research has been done on how supplementation with copper glycinate affects humans. Clinically copper gluconate is much more extensively researched that copper glycinate. The Institute of Medicine set the tolerable upper level limit for copper at 10 mg/day (Institute of Medicine (US) Panel on Micronutrients, 2001).

Supplementation with coenzyme Q10 will be of assistance. NADH dehydrogenase transfers electrons from NADH via coenzyme Q10 (ubiquinone; Ohnishi et al., 2018). Supplementing with ubiquinol, which is reduced coenzyme Q10, is avoided as NADH dehydrogenase requires coenzyme Q10 for activity. Coenzyme Q10 provides a cofactor for NADH dehydrogenase, which has iron-sulfur clusters, and is dysregulated in schizophrenia. Coenzyme Q10 is well tolerated in healthy individuals and individuals with Huntington's disease at dosages of coenzyme Q10 as high as 2400 μg/day (Huntington Study Group Pre2CARE Investigators et al., 2010).

Supplementation with pantothenic acid, acetyl-L-carnitine, and vitamin B6 will be of assistance. Coenzyme A is synthesized from pantothenic acid and L-cysteine (Leonardi and Jackowski, 2007). Due to shortages of L-cysteine, there could be difficulties in synthesizing coenzyme A. Coenzyme A is required for the synthesis of the acyl carrier protein as the acyl carrier protein derives the 4′-phosphopantetheine moiety of the acyl carrier protein from coenzyme A (Elovson and Vagelos, 1968). The acyl carrier protein is a required subunit of eukaryotic iron-sulfur cluster biogenesis (Van Vranken et al., 2016). Supplementation with pantothenic acid will support coenzyme A synthesis and iron-sulfur cluster biogenesis. There are no reports of toxicity due to pantothenic acid supplementation; however, the Institute of Medicine did not have enough information to set a tolerable upper level limit for pantothenic acid (Institute of Medicine, 1998). The acyl carrier protein is a component of fatty acid synthetase that requires acetyl-coenzyme A for activity. L-carnitine is required for the synthesis of acetyl-coenzyme A (Hoppel, 1982). The synthesis of L-carnitine requires two Fe(II) and α-ketoglutarate-dependent enzymes, ε-*N*-trimethyllysine hydroxylase (Vaz et al., 2001) and γ-butyrobetaine hydroxylase (Lindstedt and Lindstedt, 1970) whose decreased

activity would lead to shortages of L-carnitine in schizophrenia. Pantothenic acid along with acetyl-L-carnitine will support acetyl-coenzyme A synthesis and actions of the acyl carrier protein in iron-sulfur cluster formation. Acetyl-L-carnitine, when taken for Alzheimer's disease for 1 year at 3 g/day acetyl-L-carnitine, was well tolerated (Thai et al., 1996). Many enzymes involved in L-cysteine metabolism, for example, CBS, CTH, and cysteine desulfurase, are vitamin B6-dependent enzymes. Various enzymes involved in selenium metabolism are also vitamin B6-dependent enzymes (Soda et al., 1999). The Institute of Medicine has set the tolerable upper limit level for vitamin B6 at 100 mg/day for adults (Institute of Medicine, 1998).

Supplementation with whey protein will be of assistance. When CTH synthesizes L-cysteine, α-ketobutyrate is also synthesized. Propionyl-CoA is synthesized from α-ketobutyrate. Due to low levels of α-ketobutyrate, there will be low levels of propionyl-CoA. Propionyl-CoA can also be synthesized from branched-chain amino acids. Whey protein is high in branched-chain amino acids. Whey protein is also high in glutamic acid from which 2-oxoglutarate is synthesized. With the treatment, there could be an increase in gene transcription. Whey protein will support increased protein synthesis attendant on increased gene transcription. A supplement with a complete amino acid profile, such as whey protein, is preferable to taking individual amino acids as a complete amino acid supplement will not cause amino acid imbalances. Whey protein additionally contains cystine. Supplemental whey protein increases glutathione levels (Grey et al., 2003). Whey protein is very frequently supplemented (Pasiakos et al., 2015). Excessively high protein intakes, however, should be avoided.

Antioxidant supplements that do not work by being cofactors of enzymes, for example, vitamin E, β-carotene, and flavonoids, are avoided. Molybdenum-containing enzymes are oxidases. Antioxidants could decrease available O_2 decreasing activity of molybdenum-containing proteins such as SUOX and XO. Research shows that supplemental vitamin E reduces the levels of XO (Raghuvanshi et al., 2005). Other research shows that quercetin, which is an antioxidant flavonoid, inhibits XO (Zhang et al., 2016). Riboflavin is not supplemented. Flavin reductase, which reduces riboflavin, is also biliverdin reductase B (Cunningham et al., 2000). Biliverdin reductase B is involved in heme degradation (Whitby et al., 2002). Supplementation with riboflavin could competitively inhibit biliverdin reductase B and dysregulate heme degradation. Zinc is not supplemented. Zinc increases the levels of metallothionein, which is an L-cysteine-rich protein (Cousins, 1983). Increases in metallothionein levels due to supplementation with zinc could shift L-cysteine to metallothionein and away from other uses. Manganese levels should be monitored. The divalent metal transporter 1 transports both iron and manganese (Wolff et al., 2018). Manganese would be supplemented if manganese levels are low. The Institute of Medicine has set the tolerable upper level limit for manganese at 11 mg/day (Institute of Medicine (US) Panel on Micronutrients, 2001).

Research cited at least partly references clinical trials undertaken on humans, except research on molybdenum, where mostly animal studies are addressed with findings on animals then extrapolated to humans. The Institute of Medicine is associated with the National Academy of Sciences (US). The Institute of Medicine is now termed the National Academy of Medicine (US).

Conclusion

There is a great need for a new treatment option to manage TRS. Personal, familial, and societal costs associated with TRS are extremely high. Clozapine, the gold standard for TRS, has very significant side effects, which can be life threatening. As discussed above, there are five black-box warnings for clozapine. The proposed treatment, which is an add-on treatment to mainline antipsychotics, would obviate the need for patients to take clozapine and could allow reductions in dosages of mainline antipsychotics. With the proposed treatment, patients with TRS will not need to take clozapine, avoiding the side effects of clozapine. Patients being able to reduce dosages of mainline antipsychotics would be very beneficial to patients, as high dosages of antipsychotics are associated with increased side effects, such as tardive dyskinesia, diabetes, and metabolic syndrome. Negative symptoms of schizophrenia are highly prevalent; however, pharmacological treatments available now inadequately treat negative symptoms. The proposed treatment could be effective against negative symptoms.

There is a wide range of evidence that indicates that the transsulfuration pathway is dysregulated in schizophrenia. Increased homocysteine levels, decreased H_2S levels, decreased glutathione levels, decreased GPX levels, and deficits in OXPHOS in schizophrenia all point to the transsulfuration pathway being dysregulated in schizophrenia. Decreased levels of XO and decreased levels of uric acid in schizophrenia point to molybdenum-containing proteins as being dysregulated in schizophrenia where decreased levels of molybdenum-containing proteins

could be due to difficulties in synthesizing L-cysteine due to the low activity of the transsulfuration pathway. That TRS is a severe form of schizophrenia with illness severity positively associated with homocysteine levels points to the transsulfuration pathway and pathways that are dysregulated when the transsulfuration pathway is dysregulated as pathways where interventions could successfully treat TRS. Future clinical trials of the recommended supplements are the most appropriate way to investigate whether addressing dysregulations of the transsulfuration pathway and dysregulations of other pathways that can arise from dysregulations of the transsulfuration pathway can treat TRS.

There is a great deal of evidence now that the activity of the transsulfuration pathway is low in schizophrenia. The proposal put forward is that a pronounced dysregulation of the transsulfuration pathway is associated with TRS with other pathways connected to L-cysteine metabolism also dysregulated and that targeting via supplements such dysregulated pathways can ameliorate the symptoms of TRS. If the proposed treatment ameliorates the symptoms of TRS, this would point to a key area that can be researched to better understand the biological basis of schizophrenia.

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