Chapter 28
Schizophrenia, Oxidative Stress and Selenium

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Abstract Schizophrenia is a complex, crippling mental illness that is influenced by multiple environmental and genetic factors. Oxidative stress is among the most prominent factors implicated in schizophrenia. Many components of the oxidative stress pathways influence cell-signaling cascades that regulate several neurotransmitter systems. One of the characteristic features of schizophrenia is altered dopaminergic, glutamatergic, and GABAergic neurotransmission, which is influenced by oxidative stress and exacerbated by certain drugs of abuse. Selenoproteins play critical roles in defense against oxidative stress and include glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases. Based upon their integral function in protection against oxidative stress, impaired selenoprotein synthesis and function may contribute to the pathogenesis of schizophrenia.

28.1 Introduction

Selenoproteins are a unique class of proteins, which play critical roles in defense against oxidative stress. They include glutathione peroxidases (GPxs), thioredoxin reductases (TXNRDs), and iodothyronine deiodinases (DIOs). Selenoproteins are characterized by the incorporation of selenium as selenocysteine, the 21st amino acid, at UGA codons, which typically serve as stop codons [1]. The majority of selenoprotein mRNAs contain single UGA codons, which encode one selenocysteine residue per polypeptide chain. Selenocysteine residues are inserted cotranslationally by means of a selenocysteine insertion sequence (SECIS) located in the 3′-UTR (untranslated region) of selenoprotein mRNAs, which direct incorporation of this

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unique amino acid [2]. In all selenoproteins characterized to date, selenocysteine residues are catalytically active in redox processes.

The involvement of selenium in health-related processes was discovered in 1973, when selenium was found to be an essential component of the detoxifying enzyme, glutathione peroxidase (GPx) [3]. At present, 25 selenoproteins have been identified in humans, including five GPxs, three TXNRDs, and three DIOs. Genetic knockout studies in mice have demonstrated that at least three selenoproteins are essential, as deletion of thioredoxin reductase 1 (*Txnrd1*), thioredoxin reductase 2 (*Txnrd2*), or glutathione peroxidase 4 (*Gpx4*) results in embryonic lethality [4–6]. GPxs protect cells from the deleterious effects of oxidative stress by catalyzing the reduction of hydrogen peroxide (H_2O_2). The antioxidant, glutathione (GSH), is an essential cofactor that normally acts as the electron donor in enzymatic reactions involving GPxs. TXNRDs comprise a family of homodimeric flavoenzymes that catalyze the NADPH-dependent reduction of oxidized thioredoxin in cellular redox pathways. In this class of proteins, selenocysteine is incorporated as the penultimate C-terminal residue [7], where it is essential for enzymatic activity [8]. Another important class of selenoproteins is the DIOs, which catalyze the activation and inactivation of thyroid hormones by reductive deiodination, and hence, play fundamental roles in both development and maintenance of thyroid hormone homeostasis.

In addition to the aforementioned classes of characterized selenoproteins, several additional selenoproteins have been identified and the functions of these proteins have been distinguished to varying degrees. Of these, one of the most intriguing and best characterized is selenoprotein P(Sepp1). Sepp1 is distinct, due to the fact that it contains multiple selenocysteine residues (ten in humans) and has two SECIS elements in the 3′-UTR of its mRNA. It is a secreted glycoprotein that is synthesized in many tissues, with the highest level of expression occurring in the liver. Sepp1 can be divided into two functional domains, an N-terminal domain containing one selenocysteine (U) in a U-x-x-C redox motif, and a shorter C-terminal domain containing multiple selenocysteines (nine in humans) [9]. Based upon its structural characteristics, Sepp1 is widely believed to be multifunctional. The enzymatically active N-terminal domain is thought to be involved in the maintenance of extracellular redox balance, while the primary function of the selenocysteine-rich C-terminal domain is speculated to be selenium transport [10]. Sepp1 binds to the lipoprotein receptors, ApoER2 and megalin, which mediate its uptake into the brain and testis (ApoER2), and kidney (megalin), respectively [9]. In mice, deletion of selenoprotein P (*Sepp1*$^{-/-}$ mice) results in impaired motor coordination, seizures, deficits in spatial learning, and defects in synaptic plasticity [11]. Likewise, deletion of the Sepp1 receptor, ApoER2, produces many similar deficits [12].

28.2 Schizophrenia and Oxidative Stress

Schizophrenia is a neuropsychiatric condition characterized by a heterogeneous mixture of positive (hallucinations, delusions), negative (flat affect, catatonia), and cognitive (attention, memory) symptoms. This devastating disorder affects roughly

1.0% of the population, emerges during late adolescence/early adulthood, and is subject to chronic relapses with intermittent periods of remission [13]. As with most psychiatric conditions, schizophrenia appears to be influenced by a complex array of environmental and genetic variables.

One of the primary factors thought to influence the development and course of schizophrenia is oxidative stress. Reactive oxygen species (ROS), such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2), can damage neurons by means of lipid peroxidation, protein carboxylation, DNA strand breaks, and altered cell signaling. The link between oxidative stress and schizophrenia is supported by a number of both clinical and genetic studies. Decreased levels of GSH in schizophrenic patients were first noted in 1934 [14], but there was little follow-up on these initial findings. However, several recent studies have documented a correlative relationship between low GSH levels and schizophrenia. One report found a 27% reduction in cerebrospinal GSH levels [15] in untreated patients with schizophrenia, whereas another study documented a 41% decrease in GSH levels in the caudate nucleus postmortem [16]. Several recent studies have also provided genetic evidence for a link between schizophrenia and impaired GSH synthesis. A trinucleotide repeat (TNR) polymorphism in the 5′-UTR of the catalytic subunit of glutamate cysteine ligase (GCLC) was reported to be associated with schizophrenia in humans [17]. Moreover, lower GCLC expression, glutamate cysteine ligase (GCL) activity, and GSH levels were found among the subjects with genotypes that positively associated with schizophrenia. Finally, a global parallel analysis of transcripts, proteins, and metabolic intermediates in the prefrontal cortex of schizophrenia patients identified oxidative stress pathways including the GSH and thioredoxin systems, as being substantially altered [18].

28.3 Schizophrenia, Dopamine and Oxidative Stress

Altered dopamine signaling has long been implicated as a key feature of schizophrenia. Elevated dopaminergic neurotransmission was initially considered to be intrinsically related to psychosis, as dopamine-releasing drugs, such as amphetamines, induce psychosis and the first clinically effective antipsychotics antagonized dopamine receptors [19]. The dopamine hypothesis was further refined during the 1970s, when it was shown that the clinical potency of antipsychotic medication for alleviating the positive symptoms of schizophrenia was highly correlated to its ability to block dopamine D_2 receptors [20]. As additional scientific evidence accumulated and it became apparent that schizophrenia was far more complex than excessive dopaminergic neurotransmission, the role of dopamine in schizophrenia was reconceptualized in the early 1990s. In a seminal review paper, Davis and colleagues proposed a modified dopamine hypothesis of schizophrenia that added regional specificity and attempted to account for both negative and positive symptoms [21]. Based upon multiple lines of evidence from human and animal studies, the authors suggested that schizophrenia is not the result of a hyperdopaminergic brain, but rather dysregulated dopaminergic transmission in multiple brain regions.

More specifically, they hypothesized that positive symptoms are caused by enhanced striatal dopaminergic tone, whereas negative symptoms are influenced by a lack of dopaminergic transmission in frontal brain regions.

In addition to the positive and negative symptoms, patients with schizophrenia typically exhibit impaired cognition, including deficits in semantic and explicit memory, attention, working memory, and executive function [13]. Loss of dopamine signaling in the prefrontal cortex severely disrupts performance of executive tasks in nonhuman primates [22, 23] and schizophrenia patients suffer from defective executive function [24], lending support to the hypothesis that the cognitive impairments in schizophrenia result from hypoactivity in the mesocortical dopaminergic system.

Additionally, several lines of evidence indicate that levels of both dopamine and dopamine receptors are elevated in the striatum of schizophrenic patients. Increased levels of striatal dopamine and its metabolite homovanillic acid [21], of striatal uptake of dopamine [25, 26], and of amphetamine-induced dopamine release [27, 28] have all been reported in patients with schizophrenia. The increase in striatal dopamine availability in schizophrenia is coupled with an increase in striatal dopamine D_2 receptors [29, 30], but whether D_2 receptor increases are apparent before the onset of symptoms, especially during development, is uncertain. This is significant because transgenic mice that transiently overexpress the D_2 receptor within the striatum exhibit impaired performance in cognitive tests as well as increased D_1 receptor activation and decreased dopamine turnover in prefrontal cortex [31, 32]. Moreover, if overexpression is limited to developmental stages, the behavioral deficits are still exhibited in adults, implying that hyperdopaminergic signaling in the striatum during development induces compensatory changes in prefrontal cortex that last well into adulthood.

In the current genomic age, the link between altered dopamine signaling and schizophrenia has been further solidified. Multiple genes involved in dopamine signaling have been associated with schizophrenia, including *DRD2* [33, 34] and *COMT* [35, 36], providing additional evidence for dopamine dysregulation in schizophrenia. Furthermore an association of *DRD2* and *COMT* polymorphisms with impaired performance on working memory and executive function tests has been reported [37–39]. These findings support the idea that genetic susceptibility loci are functionally relevant in schizophrenic patients and for the symptoms they present.

In addition to its role in neurotransmission, dopamine is also a source of ROS in the brain, as dopamine metabolism (Fig. 28.1) produces H_2O_2 and can spontaneously generate highly reactive quinone and superoxide molecules [40]. Furthermore, elevated dopamine metabolism depletes available antioxidant defense systems and renders neurons more susceptible to the negative effects of oxidative stress. This notion is well supported by experiments performed by Do and colleagues looking into effects of dopamine on GSH levels in cultured cortical neurons [41]. In this study, dopamine application resulted in a 40% reduction in intracellular GSH content. This effect appeared to be due to the direct conjugation of dopamine semiquinone/quinone with GSH, as it was not dependent upon D_1 or D_2 receptor activation, monoamine oxidase (MAO) activity, or the generation of ROS. Additional studies

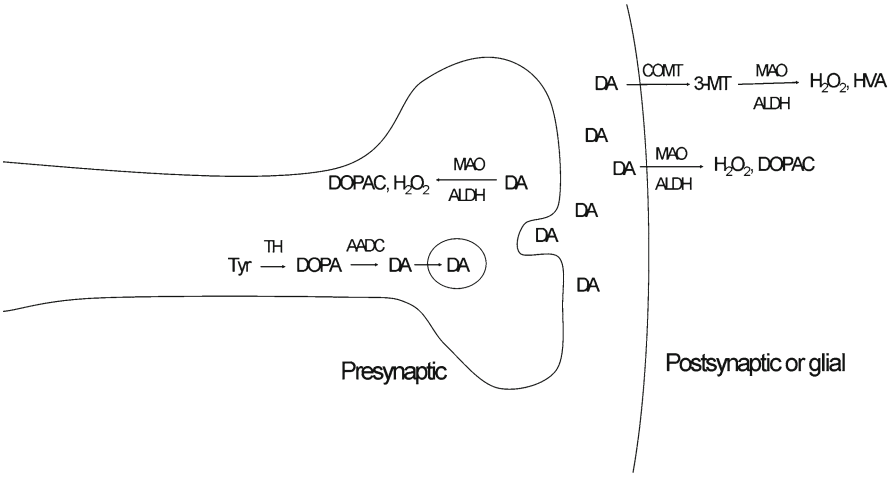

Fig. 28.1 Dopamine metabolism at the synapse. The initial step in the synthesis of dopamine (DA) is hydroxylation of tyrosine (Tyr) by tyrosine hydroxylase (TH), resulting in dihydroxyphenylalanine (DOPA). DOPA is subsequently decarboxylated by aromatic amino acid decarboxylase (AADC) to produce DA, which is sequestered into vesicles by the vesicular monoamine transporter. Presynaptic DA that is not sequestered in vesicles is catabolized primarily by monoamine oxidase (MAO). Oxidative deamination of DA by MAO generates hydrogen peroxide (H_2O_2) and an aldehyde that is subsequently oxidized by aldehyde dehydrogenase (ALDH) to its corresponding acid, dihydroxyphenylacetic acid (DOPAC). Postsynaptic and glial metabolism of DA are similar, with an additional route, whereby DA is first methylated by catechol-O-methyltransferase (COMT) generating 3-methoxytyramine (3-MT). As before, oxidative deamination of 3-MT by MAO generates peroxide and an aldehyde that is oxidized by ALDH to homovanillic acid (HVA). Note that the aldehyde intermediates and the membrane transporters have been omitted for clarity

using ethacrynic acid (EA), an inhibitor of glutathione-S-transferase, decreased GSH levels in a dose-dependent manner. Combined application of dopamine and EA further diminished GSH levels and this additional decrement was inhibited by either D_1/D_2 receptor or SOD antagonists, suggesting a mechanism involving the activation of dopamine receptors and the generation of superoxide. Coadministration of both dopamine and EA for a period of 24 h was also found to result in a 30% reduction in the number of neuronal processes. These results provide evidence for a functional relationship between dopamine and GSH that influences neuronal connectivity.

28.4 Schizophrenia, NMDA Receptors and Oxidative Stress

In recent years, extensive evidence has demonstrated that glutamatergic signaling is also dysregulated in schizophrenia and this appears to be largely due to compromised function of NMDA receptors (NMDARs). Hypofunction of NMDARs is thought to be a key facet of schizophrenia, as administration of NMDAR antagonists,

such as ketamine and phencyclidine (PCP), induce a psychotic state in humans similar to schizophrenia [42]. This notion is further substantiated by findings that transgenic mice containing mutations in NMDAR subunits exhibit some behaviors analogous to schizophrenia [43, 44] and by reports that pharmacological enhancement of NMDAR function can alleviate human schizophrenic symptoms [45]. Additional support is provided by postmortem studies reporting reduced expression of the NR2A subunit in schizophrenic patients [46, 47].

There also appears to be a distinct relationship between oxidative stress and NMDA-dependent synaptic plasticity. NMDA receptors have extracellular redox-sensitive sites, by which reducing agents, such as GSH, can enhance function [48, 49]. Recent experiments on tissue slices of the rat hippocampus provide evidence that GSH deficits alter synaptic transmission [50]. In this study, a 40% decrease in brain GSH levels was induced via administration of an inhibitor of GSH synthesis. This resulted in enhanced excitability and impaired NMDAR-dependent long-term potentiation (LTP) in GSH depleted slices. These findings demonstrate that oxidative stress can impair the function of NMDA receptors.

Interestingly, NMDAR hypofunction has also been associated with increased glutamatergic neurotransmission [51, 52]. Specifically, in vivo microdialysis experiments revealed that systemic administration of low doses of ketamine produce elevated glutamate levels in the prefrontal cortex [53]. In turn, elevated levels of extracellular glutamate can have adverse effects on antioxidant defense mechanisms. Increased levels of glutamate have been shown to inhibit the uptake of cystine [54], a required precursor for GSH synthesis [55]. Glutamate also acts postsynaptically on both NMDARs and non-NMDA ionotropic AMPA and kainate receptors, triggering the accumulation of cytosolic calcium. Excessive intracellular calcium has multiple potential deleterious effects, such as the activation of catabolic enzymes and the generation of free radicals [56]. In sum, elevated extracellular glutamate levels may lead to intracellular calcium overload, enhanced production of ROS, and a hyperexcitable brain that is more susceptible to seizures.

28.5 Schizophrenia, Parvalbumin Interneurons and Oxidative Stress

Another characteristic feature of schizophrenia is dysfunctional cortical inhibition. Individuals with schizophrenia exhibit altered neural oscillations [57] and show reduced expression of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD67) upon postmortem examination [58]. The link between cortical inhibition and schizophrenia is further supported by the finding that single nucleotide polymorphisms in the regulatory region of *GAD1* (gene coding for GAD67) are correlated with an early onset of schizophrenia [59]. The decrease in GAD67 levels commonly observed in schizophrenia occurs mainly in a subset of interneurons expressing the calcium-binding protein, parvalbumin (PV) [60, 61]. PV-positive interneurons control the firing rates of pyramidal neurons and are critically involved

in generating gamma frequency neural oscillations [62–64]. It has been proposed that the impaired cortical inhibition characteristic of schizophrenia may be a result of flawed maturation of PV-interneurons caused by excessive oxidative stress during neurodevelopment [65]. This idea is corroborated by recent findings that deletion of the gene coding for the modifier subunit of glutamate cysteine ligase (GCLM), a rate-limiting enzyme for GSH synthesis, results in reduced numbers of PV-interneurons and altered gamma oscillations in the ventral hippocampus [66].

Several contemporary reports demonstrate that NMDAR hypofunction and dysfunctional cortical inhibition are intricately intertwined. Experiments in cultured interneurons, wherein the NMDAR antagonist, ketamine, was applied at sublethal concentrations, revealed a time- and dose-dependent decrease in GAD67 and PV immunoreactivity [67]. Repeated in vivo exposure to NMDAR antagonists has also been demonstrated to decrease PV expression in rodents [68] and nonhuman primates [69]. Additionally, electrophysiological studies found that inhibitory GABAergic interneurons were approximately tenfold more sensitive to the effects of NMDAR blockade than excitatory pyramidal neurons [70]. This suggests that the intriguing pairing of NMDAR hypofunction with increased glutamatergic neurotransmission may be the result of insufficient activation of NMDARs on inhibitory GABAergic interneurons. The notion that NMDA hypofunction on GABAergic interneurons is a key component of schizophrenia is further supported by recent studies in which the NR1 subunit was selectively eliminated on PV-interneurons during the early postnatal period [71]. These mutant mice were impaired in several rodent behavioral assays thought to correlate with schizophrenia, including deficits in social recognition, prepulse inhibition (PPI), and spatial working memory.

28.6 Schizophrenia, Oxidative Stress and Selenium

While accumulating evidence provides support for an interconnected relationship between oxidative stress, dopamine signaling, NMDAR function, and cortical inhibition in the symptoms of schizophrenia, reports on the involvement of selenium and selenium-related proteins in schizophrenia are limited. Selenium is a necessary component of glutathione peroxidases and GPx levels have been demonstrated to correlate with whole blood selenium levels up to 0.100 ug/mL, above which GPx levels plateau [72]. In groups of patients with schizophrenia receiving treatment with antipsychotic medication, significantly reduced GPx activity has been reported [73, 74]. Of additional significance, an inverse relationship between blood GPx activity and structural assessments of brain atrophy has also been observed in a population of patients with chronic schizophrenia, suggesting a potential relationship between redox dysregulation and neurodegeneration [75].

There is also circumstantial evidence suggesting that altered function of the mitochondrial selenoprotein, thioredoxin reductase 2 (*TXNRD2*), may contribute to schizophrenia. *TXNRD2* is located on chromosome 22q11.2, a region highly implicated in schizophrenia that also contains the *COMT* gene. A hemizygous deletion of

a 3-Mb region of chromosome 22q11 occurs in approximately 1 in 4,000 humans and produces 22q11 deletion syndrome [76]. Individuals with 22q11 deletion syndrome typically exhibit cardiovascular defects, craniofacial abnormalities, and impaired cognition, as well as an increased likelihood to develop schizophrenia. Moreover, *TXNRD2* has also been reported to be significantly upregulated in the prefrontal cortex of patients with schizophrenia [18].

Of further potential significance within the United States, higher incidences of schizophrenia have been reported in states with low levels of selenium in the food chain [77]. Soil selenium concentration and the long-term rate of schizophrenia have been investigated and although there is a significant relationship, the association is not entirely consistent [78]. In addition, impaired selenium transport was previously hypothesized to be a risk factor for a subtype of schizophrenia characterized by negative symptoms [79], which is supported by findings that platelet and erythrocyte GPx activity is reduced in schizophrenic patients [80, 81].

Several studies also provide convergent evidence for altered dopaminergic signaling in response to dietary selenium intake, suggesting a potential indirect relationship to schizophrenia. Dietary selenium deficiency elevates and prolongs high potassium-induced dopamine release in the striatum, and increases the turnover rate of dopamine in the substantia nigra, prefrontal cortex, and hippocampus [82–85]. Furthermore, selenium deficiency upregulates both tyrosine hydroxylase and dopamine transporter mRNAs in nigrostriatal neurons, with concomitant increases in dopamine synthesis and uptake [86]. Conversely dietary Se supplementation reduces the activity of the dopamine catabolic enzyme, monoamine oxidase (MAO) [87]. Additionally, dopamine deamination by MAO generates H_2O_2, and MAO-catalyzed peroxide generation is coupled to the enzymatic activity of the selenoprotein, GPx1 [88]. Collectively, these findings suggest that dietary selenium modulates the turnover and metabolism of dopamine, which may profoundly affect the pathogenesis of schizophrenia. However, recent genome wide association studies have not identified any polymorphisms in selenoprotein coding genes that significantly associate with schizophrenia.

Nevertheless, studies on mice with targeted disruption of selenoprotein expression provide some intriguing parallels with endophenotypes of human schizophrenia patients. Transgenic mice with neuron-specific deletion of selenoprotein biosynthesis (*Tα1-Cre/Trsp*$^{fl/fl}$) exhibit growth defects and lack of postural control, and rarely survive past P12 [89]. When Cre-mediated recombination is restricted to forebrain neurons (*CamK-Cre/Trsp*$^{fl/fl}$), the mutant mice are able to walk, albeit poorly, and their life span is only moderately extended to P13–P15. Further experiments on *CamK-Cre/Trsp*$^{fl/fl}$ mutants revealed dysfunctional development of the GABAergic system, as PV-interneurons failed to develop and spontaneous epileptiform activity was observed in hippocampal slice preparations of P10 animals. In additional studies, the researchers generated *CamK-Cre/Gpx4*$^{fl/fl}$ mutant mice in order to assess the effects of forebrain-specific GPx4 deletion and compare with a complete blockade of selenoprotein synthesis. In comparison to *CamK-Cre/Trsp*$^{fl/fl}$ mutants, *CamK-Cre/Gpx4*$^{fl/fl}$ mice exhibit similar deficits, albeit milder, as these mice are hyperexcitable, display an awkward gait, and have reduced numbers of

PV-interneurons on P13. In summary, these results indicate a critical role for GPx4 in the development of PV-interneurons [89]. These findings may have particular relevance for schizophrenia, given the established relationship between oxidative stress and impaired cortical inhibition.

Selenium appears to be particularly critical for proper brain function, as selenium is preferentially retained under conditions of selenium deficiency and upon selenium reintroduction into the diet, the brain is the first organ to be re-supplied [90, 91]. In the brain, the primary means of selenium delivery is via ApoER2-mediated uptake of selenoprotein P (Sepp1) [9]. Transgenic mice with targeted deletion of Sepp1 have diminished levels of selenium and reduced GPx and TXNRD activity in the brain [92, 93]. *Sepp1*$^{-/-}$ mice also display a distinct neurological phenotype, which includes occasional seizures, motor dysfunction, and accelerated neurodegeneration [94, 95]. Although administration of a high selenium diet (1 mg/kg) from birth can attenuate many of the adverse symptoms of Sepp1 deletion, *Sepp1*$^{-/-}$ mice maintained on a high selenium diet exhibit motor incoordination, impaired spatial learning, and altered synaptic plasticity in the hippocampus [11]. These findings suggest that Sepp1 may directly influence synaptic plasticity, most likely via the ApoER2 receptor. Transgenic mice without a functional ApoER2 receptor exhibit several symptoms analogous to those of *Sepp1*$^{-/-}$ mice, including reduced brain selenium levels, deficits in spatial learning, and impaired LTP in the hippocampus [11, 12, 92, 93, 96]. Within the membrane, the ApoER2 receptor forms a complex with several signaling proteins, including NMDARs, postsynaptic density protein of 95 kDa (PSD-95), and Disabled-1 (Dab-1) [96, 97]. In addition to Sepp1, several additional ligands interact with ApoER2, including ApoE and Reelin [98]. By means of stimulation of the ApoER2 receptor, Reelin critically influences both neuronal migration and synaptic plasticity and, in recent years, the Reelin signaling pathway has been extensively characterized [96–99]. In particular, an alternatively spliced intracellular domain of ApoER2 has been shown to be required for Reelin-mediated modulation of LTP and synaptic plasticity [96]. This alternatively spliced transcript encodes a 59 amino acid sequence, which contains binding sites for PSD-95 and JNK interacting proteins. Yet, further studies revealed that this intracellular domain was not required for selenium uptake, demonstrating independent roles for this domain in cell signaling and selenium transport [100]. It remains to be determined whether Sepp1 acts as a signaling protein in addition to its role in selenium delivery.

Preliminary findings in this laboratory suggest that Sepp1 may influence PV-interneuron function. Immunohistochemical evidence indicates that the ApoER2 receptor is expressed on PV-interneurons in several brain regions, including the hippocampus, medial septum, and cingulate cortex. As impaired cortical inhibition appears to be one of the cardinal features of both *Apoer2*$^{-/-}$ and *Sepp1*$^{-/-}$ mice, this phenotype may result in part from a disturbance in ApoER2-mediated delivery of Sepp1 to PV-interneurons. Impaired selenium delivery would lead to diminished selenium content, deficient selenoprotein synthesis, and elevated oxidative stress in PV-interneurons (Fig. 28.2).

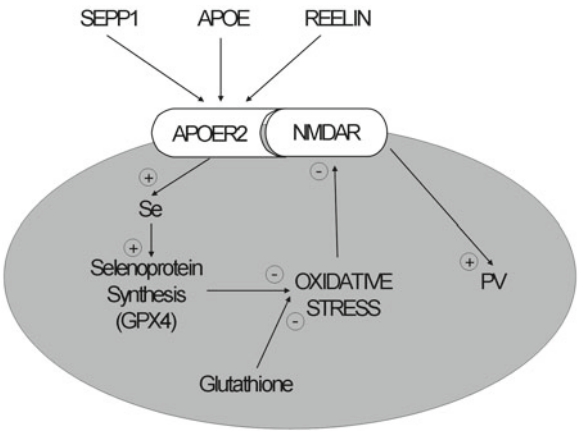

Fig. 28.2 Putative model of PV-interneuron function and oxidative stress. Selenoprotein P (Sepp1), ApoE, and Reelin all interact with the ApoER2 receptor. Preliminary data indicate that ApoER2 is expressed in PV-interneurons. ApoER2-mediated uptake of Sepp1 may act as a mechanism to provide selenium for selenoprotein synthesis in PV-interneurons. Selenoproteins, of which GPx4 is essential, protect against oxidative stress. The antioxidant, glutathione (GSH), is an essential cofactor for the glutathione peroxidases and low GSH levels have been implicated in schizophrenia. Elevated oxidative stress impairs NMDA-mediated neurotransmission, which, in turn, leads to diminished expression of parvalbumin (PV)

Additional evidence suggests that administration of selenium compounds may be preventive against psychosis. Administration of the organic selenium compound $[(F_3CPhSe)_2]$ was found to attenuate apomorphine-induced stereotypy in mice, an animal model of psychosis [101]. Of further potential relevance, upregulation of the selenium-binding protein (*SELENBP1*) has been reported in both the blood and brain of schizophrenic patients [102]. *SELENBP1* does not contain a selenocysteine residue and its functional role in the brain is currently unclear. Yet, given the fact that it binds selenium, *SELENBP1* may reduce levels of free selenium that are available for incorporation into selenoproteins. Thus, increased levels of *SELENBP1* may result in diminished selenoprotein synthesis and elevated oxidative stress. Further experimentation is required to adequately assess this possibility.

28.7 Conclusion

In summary, extensive evidence demonstrates an interconnected relationship between oxidative stress, dopamine dysregulation, NMDA hypofunction, and impaired cortical inhibition in schizophrenia. As selenoproteins comprise one of the key lines of defense against oxidative stress, compromised selenoprotein function may contribute to the dysregulated neurotransmission, impaired cognition, and

behavioral alterations that are characteristic of schizophrenia. The current evidence for the involvement of selenium-related proteins in schizophrenia is suggestive, but limited. Genetic association studies have yet to identify a single selenoprotein as a candidate gene for schizophrenia, but genetic polymorphisms and/or copy number variations in multiple selenoprotein coding genes may, in part, determine the capability of the antioxidant defense system and, thus, may either predispose or protect against the development of schizophrenia. Moreover, selenoprotein functionality may also be influenced by genetic variation in nonselenoprotein coding genes that impact the bioavailability of selenium and the synthesis of selenoproteins. In order to better distinguish the potential relationship between schizophrenia and selenium, additional research is needed to both characterize selenium-related proteins and probe human genetic variation in selenium-related genes.

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