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FORUM REVIEW ARTICLE

Antioxidants, Redox Signaling, and Pathophysiology in Schizophrenia: An Integrative View

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Abstract

Schizophrenia (SZ) is a brain disorder that has been intensively studied for over a century; yet, its etiology and multifactorial pathophysiology remain a puzzle. However, significant advances have been made in identifying numerous abnormalities in key biochemical systems. One among these is the antioxidant defense system (AODS) and redox signaling. This review summarizes the findings to date in human studies. The evidence can be broadly clustered into three major themes: perturbations in AODS, relationships between AODS alterations and other systems (*i.e.*, membrane structure, immune function, and neurotransmission), and clinical implications. These domains of AODS have been examined in samples from both the central nervous system and peripheral tissues. Findings in patients with SZ include decreased nonenzymatic antioxidants, increased lipid peroxides and nitric oxides, and homeostatic imbalance of purine catabolism. Reductions of plasma antioxidant capacity are seen in patients with chronic illness as well as early in the course of SZ. Notably, these data indicate that many AODS alterations are independent of treatment effects. Moreover, there is burgeoning evidence indicating a link among oxidative stress, membrane defects, immune dysfunction, and multineurotransmitter pathologies in SZ. Finally, the body of evidence reviewed herein provides a theoretical rationale for the development of novel treatment approaches. *Antioxid. Redox Signal.* 15, 2011–2035.

Introduction

Schizophrenia (SZ) is a major mental disorder that typically strikes in adolescence or early adulthood, and continues throughout the life span (256). Its prevalence is equal across all cultures, and it affects ~1% of the general population worldwide (107, 124). SZ is characterized by a positive syndrome consisting of symptoms such as hallucinations, delusions, and paranoia, as well as a negative syndrome marked by alogia, anhedonia, avolition, and blunted affect (252, 262). SZ has been linked to widespread structural and functional brain alterations, the pathogenesis of which remains poorly understood.

The vast majority of research into the pathogenesis of SZ has thus far focused on the dopamine system. However, evidence for dopaminergic alterations in SZ is largely indirect, and is based on the fact that most antipsychotic medications act as antagonists at the dopamine receptor, particularly D_2 (31, 119, 247). A host of alternative hypotheses regarding the pathophysiology of SZ have therefore been proposed over the years to conceptualize the pathophysiology of SZ. These include neuronal maldevelopment, impaired neurotransmission, role of viral infections, autoimmune dysfunction, and many others. Although there are a variety of apparently disparate biological findings reported in SZ (110, 141, 236), it is possible that there is etiologic heterogeneity, in which multiple etiological factors converge on a final common pathogenetic pathway (or very few pathways) may mediate the recognizable syndromes of SZ. The issue at hand, therefore, is to identify candidate pathological process(es) that account for the constellation of clinical and biological features in SZ patients.

Free radicals are highly reactive chemical species generated during normal metabolic processes, which in excess can lead to membrane damage. Elaborate antioxidant defense systems exist to protect against oxidative stress. There is increasing evidence of antioxidant defense system (AODS) deficits in SZ (13, 27, 53, 66, 89, 147, 154, 157, 191, 204, 216, 293). Membrane dysfunction can be secondary to free radical-mediated pathology, and may contribute to specific aspects of SZ

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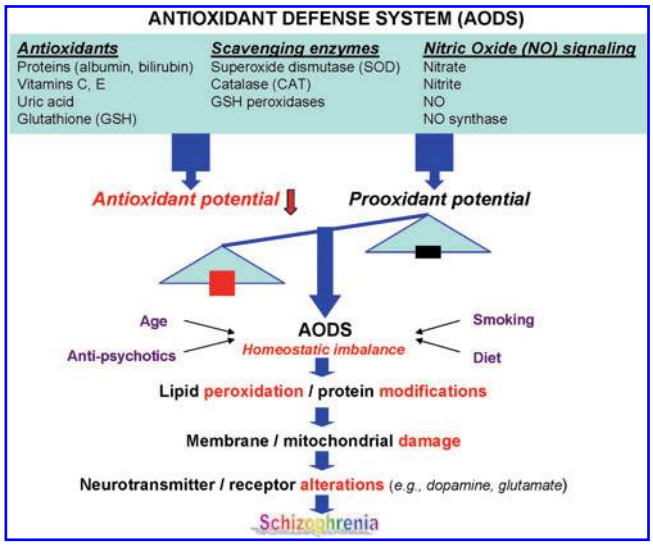

FIG. 1. A schematic diagram linking homeostatic imbalance in antioxidant defense system to pathophysiology in schizophrenia (SZ). (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

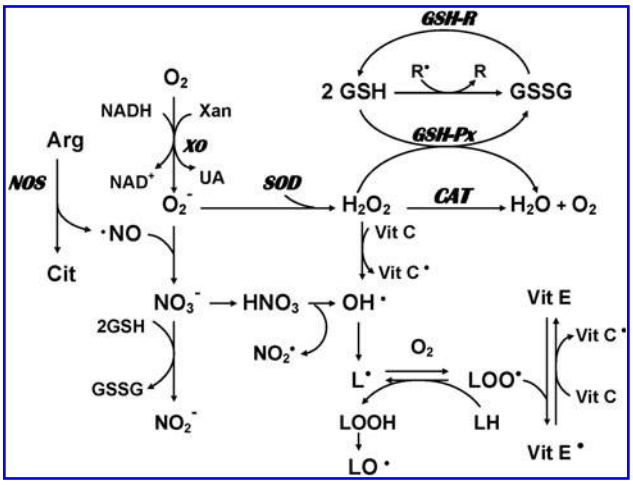

FIG. 2. Possible mechanisms involving production and removal of oxygen and nitrogen free radicals in mammalian cells. Molecular oxygen can be converted to superoxide radicals ($O_2^{-}\bullet$) in the presence of xanthine oxidase (XO). Subsequently, superoxide dismutase (SOD) catalyzes the conversion of superoxide radicals to hydrogen peroxide (H_2O_2). Catalase (CAT) and glutathione peroxidase (GSH-Px) convert hydrogen peroxide to water. Glutathione (GSH) is utilized by GSH-Px to yield the oxidized form of glutathione (GSSG), which is converted back to GSH by glutathione reductase (GR). Hydrogen peroxide is susceptible to autoxidation to form hydroxyl radicals (OH•), particularly in the presence of metal catalysts such as iron. In addition, nitric oxide (NO), which is the product of a five-electron oxidation of the amino acid L-arginine, can also produce hydroxyl radicals as well as nitrogen dioxide radical. On the other hand, α-tocopherol (vitamin E) has the ability to inhibit lipid peroxidation as a chain-breaking antioxidant. Vitamin E radicals can be recycled back to their native form by ascorbic acid (vitamin C).

symptomatology and complications of its treatment. A diagram linking AODS imbalance to SZ pathology is illustrated in Figure 1. Specifically, free radical-mediated abnormalities may contribute to the development of a number of clinically significant consequences, including prominent negative symptoms, tardive dyskinesia, neurological signs, and Parkinsonian symptoms. The aim of this article is to provide a comprehensive review of recent research in antioxidant defense system and its possible role underlying the neuropathogenetic mechanism of SZ.

Free radicals

Free radicals are reactive chemical species generated during normal metabolic processes involving oxygen and nitric oxide (Fig. 2), including the mitochondrial electron transfer chain, nicotinamide adenine dinucleotide phosphate-dependent oxidase, and autooxidation of polyunsaturated fatty acids (PUFAs) and catecholamines (90, 221). These free radicals (primarily the reactive oxygen species [ROS], superoxide, and hydroxy radicals) play an important role in membrane lipid peroxidation.

There are multiple pathways leading to excessive free radical generation and subsequent oxidative stress. In addition to the superoxide and hydroxyl radicals, another pathway is the formation of peroxynitrite by a reaction of nitric oxide radical and superoxide radical (Fig. 2). Nitric oxide (NO) can also produce hydroxyl radicals as well as nitrogen dioxide radicals. Nitric oxide is a free radical by its unpaired electron. Since NO radicals cannot produce initiation or propagation reactions, they do not generate free radical chain reactions. However, NO is a unique second messenger molecule that mediates a number of cellular functions, including neurotransmission, neurotoxicity and plasticity, vasodilation, regulation of blood flow, and inhibition of platelet aggregation (22, 105, 174). Elevated NO production has been linked to various neurodegenerative disorders, including Alzheimer's disease (186, 255), multiple sclerosis (94), and Parkinson's disease (19, 81, 103).

Antioxidant defense system

Biological systems have evolved complex protective strategies against free radical toxicity. Under physiological conditions the potential for free-radical-mediated damage is kept in check by the AODS, which is comprised of a series of enzymatic and nonenzymatic components. The critical antioxidant enzymes include superoxide dismutase (SOD; E.C.1.15.1.6), catalase (CAT; E.C.1.11.1.6), and glutathione peroxidase (GSH-Px; E.C.1.11.1.9). These enzymes act cooperatively at different sites in the metabolic pathway of free radicals (Fig. 2). Hydrogen peroxide produced by SOD is decomposed to water and oxygen by the heme protein, CAT, thereby preventing the formation of hydroxy radicals. Failure of this first-line antioxidant defense may lead to an initiation of lipid peroxidation. Selenium-dependent GSH-Px protects against lipid peroxidation by converting hydrogen peroxide to water, or more critically by converting toxic hydroperoxides to less toxic alcohols. Since SOD, CAT, and GSH-Px are critical to different stages of free radical metabolism, altered activity of one enzyme without compensatory changes in other enzymes may leave the membranes vulnerable to damage. Thus, the differential patterning of the antioxidant enzyme activities may provide important clues to the pathogenetic mechanisms of abnormal free radical metabolism (237).

In addition, the nonenzymatic antioxidant components, which may be equally important in the overall AODS (Fig. 2), consist of molecules that react with activated oxygen species and thereby prevent the propagation of free radical chain reactions. The most common nonenzymatic antioxidant molecules are albumin, uric acid, bilirubin, GSH, ascorbic acid (vitamin C), and α-tocopherol (vitamin E).

Altered AODS in SZ

Oxidative stress is a state when there is a dysequilibrium between pro-oxidant processes and the antioxidant defense system in favor of the former. There are potentially multiple pathological consequences of increased oxidative stress, due to increased free radical production and/or inefficient antioxidant systems (*e.g.*, increased SOD and/or decreased CAT activity), which lead to lipid peroxidation. It has been suggested that increased scavenging activity of SOD in the absence of increased superoxide production can depress free radical-dependent reactions, such as those catalyzed by oxygenases (11), thus resulting in decreased catecholamine production. We review below the literature on AODS supporting a role of oxidative stress in SZ pathology (Table 1).

Decreased individual antioxidants in plasma

Albumin, uric acid, and ascorbic acid substantively contribute (>85%) to the total antioxidant capacity in human plasma (271**)** largely due to their high concentrations relative to those of other antioxidants in blood, for example, GSH, bilirubin, ascorbic acid (vitamin C), and α-tocopherol (vitamin E).

Proteins. Albumin and bilirubin are both metal-binding proteins with free radical scavenging properties. Albumin inhibits lipid peroxidation by binding copper ions and also serves as a scavenger of both oxygen- and carbon-centered free radicals (71, 238). Bilirubin, though less abundant, is a more efficient antioxidant than albumin. Plasma albumin and total bilirubin are reduced in early and chronic SZ (Table 1). Consequently, urinary excretion of biopyrrins (*i.e.*, oxidative metabolites of bilirubin) is increased. In addition, serum thioredoxin, a redox-regulating protein with antioxidant activity, can be released from cells in response to oxidative stress (183). Increased levels of serum thioredoxin have been shown in first-episode, but not chronic SZ (301).

Earlier studies noted that SZ patients had a significantly higher frequency of hyperbilirubinemia than patients with other psychosis (172, 179). To eliminate the potential confounding effects of liver function, a recent case–control study by Vitek *et al.* (268) demonstrated that serum bilirubin levels were markedly lower in SZ patients with physiological range of liver function tests than those age- and gender-matched controls. These authors suggest that increased bilirubin consumption may be resulted from an increased oxidative stress accompanying SZ.

Uric acid. Uric acid (UA), an endproduct of purine catabolism in humans, is mainly synthesized from adenine- and guanine-based purines by the enzyme xanthine oxidase (Fig. 3). The blood levels of UA depend upon the dietary intake of purines, biosynthesis of UA, and the rate of UA excretion (138, 176). UA is a selective antioxidant that removes superoxide by preventing the degradation of SOD and subsequently inhibits its reaction with NO to form peroxynitrite (260). UA can also neutralize peroxynitrite (125) and hydroxyl radicals (12, 46) to inhibit protein nitration (192) and lipid peroxidation (181), respectively. UA, *via* astroglia, may protect dopaminergic neurons from glutamate toxicity (60). In addition, UA prevents the propagation of oxidative stress from the extracellular to the intracellular milieu by preserving the integrity of the plasma membrane at the lipid–aqueous interface (87). High K^+-induced depolarization amplifies neuroprotection provided by UA through a mechanism involving Ca^{2+} elevation and extracellular signal-regulated kinases ½ activation (Fig. 4). Thus, decreased plasma UA may reflect decreased ability to prevent superoxide and peroxynitrite from damaging cellular components (138).

At increased levels, however, UA may also be considered as a marker of oxidative stress (12, 248) due to accumulation of ROS (104). Abnormally high plasma (or serum) UA has been related to cardiovascular disease, gout, hypertension, and renal disease (21, 36, 72, 112, 120), whereas low levels of plasma (or serum) UA have been linked to Alzheimer's disease, multiple sclerosis, optic neuritis, and Parkinson's disease (20, 38, 131, 133, 257). Although some studies have indicated that UA may play a role in the development or progression of such diseases (21, 112, 120, 226, 270), it remains unclear whether an increased UA contributes to the cause or is simply a consequence of these pathologic conditions (138). In short, UA can be served as both anti- and prooxidant in the AODS (Fig. 4). Plasma UA levels are reduced in chronic as well as first-episode neuroleptic-naïve patients with SZ (Table 1).

Vitamins. Ascorbic acid is a biological antioxidant that acts as a chain-breaking scavenger for peroxy radicals and acts synergistically with vitamin E (Fig. 2). Basal ganglia, which are rich in dopamine and glutamate, are also rich in ascorbic acid (188); the antioxidant function of ascorbic acid may thus protect against dopamine- or glutamate-induced neurodegenerative process (214). Both plasma and urinary vitamin C levels are decreased in SZ, relative to normal controls, even after controlling for diet. After vitamin C supplementation for 1 month, group differences were no longer significant (249). Some (44, 234), though not all (263), studies suggest that add-on supplementation of vitamin C may reduce oxidative stress and improve the outcome of SZ. Vitamin C requirements for schizophrenic patients may be higher than for normal subjects because they consumed substantially less antioxidant vitamins (C and E) and dietary fiber than a matched control group (159).

The fat-soluble vitamin E is involved in oxidative metabolism (Fig. 2) and is associated with diseases linked to oxidative stress. Brown *et al.* (23) reported decreased lipid-corrected vitamin E levels in SZ with tardive dyskinesia, relative to healthy controls, but not in patients without dyskinesia. However, there are no antioxidant monotherapy treatment trials for SZ treatment, and such a trial is unlikely to be ever conducted in the absence of demonstrable primary antipsychotic activity of an antioxidant molecule (215).

Reduced total antioxidant status in plasma

Although individual antioxidants play a specific role in the AODS, these antioxidants may act cooperatively *in vivo* to

Table 1. Alterations of Antioxidant Defense System in Patients with Schizophrenia

AODS	SZ population	Source	Findings	References	Implications/comments
Antioxidants					
Proteins					
Albumin, Bilirubin	First-episode, neuroleptic-naive	Plasma	Decrease	194, 220	Increased bilirubin consumption may be secondary to oxidative stress.
	Chronic	Plasma	Decrease	194, 268, 275, 290, 292	
Biopyrrins	Chronic	Urine	Increase	173	Biopyrrins are oxidative metabolites of bilirubin.
Thioredoxin (TRX)	First-episode, neuroleptic-naive	Serum	Increase	301	Serum TRX levels were also positively correlated with positive symptoms of Positive and Negative Syndrome Scale. Following antipsychotic treatment, reduced TRX levels may provide us with biochemical index of therapeutic outcome.
UA	First-episode, neuroleptic-naive	Plasma	Decrease	219, 284	The potential for steady formation of antioxidant UA from purine catabolism is altered early in the course of SZ (284). UA and inosine (precursor of UA) may be beneficial in the treatment of oxidative stress related neurodegenerative diseases (60, 97, 144, 229, 241).
	Chronic, treated	Plasma	Decrease	289	
Vitamins					
Ascorbic acid	Chronic	Plasma	Decrease	43, 249	Some (44, 234), though not all (263), studies suggest that add-on supplementation of vitamin C may reduce oxidative stress and improve the outcome of SZ.
		Urine	Decrease	249	
Tocopherol	SZ with tardive dyskinesia	Plasma	Decrease	23	Vitamin E levels in plasma were corrected for total lipids.
Glutathione	Untreated	Plasma	Decrease	212	Adjunctive *N*-acetyl cysteine, a precursor for GSH synthesis, may provide us with a novel therapeutic intervention targeting GSH Dysregulation in SZ (15, 139).
	Chronic	Plasma	Decrease	51	
		CSF	Decrease	54	
		Prefrontal cortex	Decrease	54	
		Postmortem caudate	Decrease	286	
Free thiols	Chronic	Serum	Decrease	101	
	Chronic	Platelets	Decrease	49	
Scavenging enzymes					
Superoxide dismutase	Chronic	Serum	Increase	43, 75, 137, 306	
		RBC	Increase	1, 169, 217, 289, 305	
		Platelets	Decrease	50	
		Postmortem brain	Increase	168	
	Chronic, untreated	RBC	Increase	290	
	Children, untreated	Platelets	Decrease	84	
	Early course, untreated	Blood	Increase	129	
		RBC	Decrease	177, 212	With progression of the illness, the superoxide dismutase levels may rise as a compensatory response to oxidative stress (177).

(*continued*)

Table 1. (Continued)

AODS	SZ population	Source	Findings	References	Implications/comments
	Treated	RBC	Decrease	212	
CAT	Untreated	RBC	Decrease	212	
	Treated	RBC	Decrease	212	
GSH peroxidase	Chronic, treated	RBC	Decrease	85, 169, 193, 212	
	Untreated	RBC	Decrease	1	
		Plasma	Increase	307	
	Neuroleptic-naive	Plasma	Increase	307	
NO signaling					
NOS activity	Chronic	Postmortem cerebral cortex	Decrease	277	In light of inconsistent findings, it is surmised that NO and its metabolites may not be of diagnostic value to distinguish SZ from healthy controls or other brain disorders.
		Platelets	Increase	45	
NOS concentration	Chronic	Postmortem cerebellar vermis	Increase	122	
Neuronal NOS expression	Chronic	Postmortem prefrontal cortex	Increase	9	
Neuronal NOS expression	Chronic	Hypothalamus	Decrease	16	
NO	Chronic	Postmortem caudate	Increase	287	
		Serum	Increase	253	
		Plasma	Decrease	140, 184	
		RBC	Increase	96	
NO_2^-, NO_3^-	Chronic	CSF	Decrease	213	
NO_2^-	Chronic	Plasma	Increase	308	
		Plasma	Decrease	279	
NO_3^-	Chronic	Plasma	Decrease	250	
Lipid peroxidation					
Thiobarbituric acid reactive species (TBARS)	Chronic	Blood	Increase	3, 65, 75, 85, 88, 137, 189, 193, 198, 207, 208, 302	Findings to date suggest that oxidative stress occurs at very early in the course of illness, and independent of treatment. However, few other studies from Scottish SZ Research Group (230) and Skinner *et al.* (235) do not support the view that increased lipid peroxidation is associated with the SZ *per se*.
	First-episode, neuroleptic-naive	Plasma	Increase	153	
	Chronic	Platelets	Increase	50	
	SZ with tardive dyskinesia	CSF	Increase	146	
Pentane	Chronic	Breath	Increase	134, 202	
Ethane	Chronic	Breath	Increase	211	
Isoprostanes	Chronic	Urine	Increase	52	
Protein modifications					
3-Nitrotyrosine	Chronic	Plasma	Increase	51	
		Platelets	Increase	49	
4-hydroxynonenal	Chronic	Postmortem anterior cingulate	Increase	269	

CSF, cerebrospinal fluid; GSH, glutathione; NOS, nitric oxide synthase; RBC, red blood cell; SZ, schizophrenia; UA, uric acid.

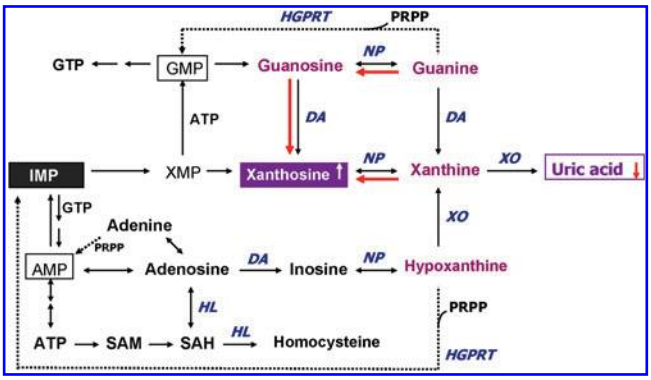

FIG. 3. Altered purine catabolism in first-episode neuroleptic-naïve patients with SZ. *Red arrows* indicate shifts toward an increase of xanthosine and a decrease of uric acid productions in first-episode neuroleptic-naïve patients with SZ patients at baseline. Reactions shown with *dotted lines* represent the salvage pathways, which purine bases can be reutilized resulting in considerably energy saving for the cell. Reprinted with permission from Yao *et al.* (284). (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

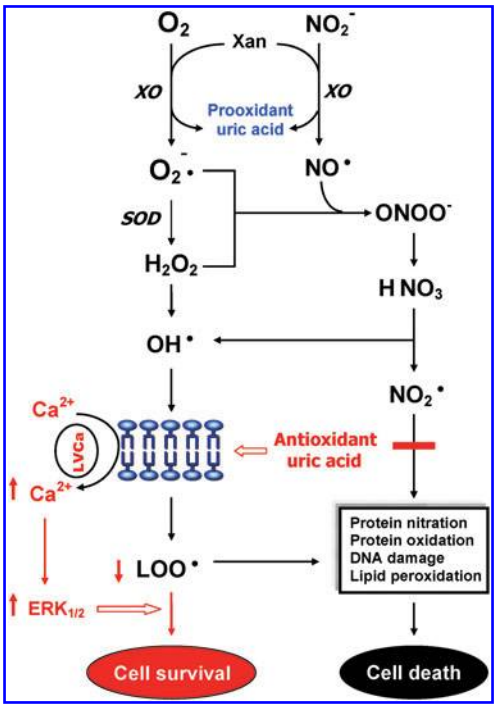

FIG. 4. Dual role of uric acid in the antioxidant defense system. Uric acid can neutralize peroxynitrite and hydroxyl radicals to inhibit protein nitration and lipid peroxidation, respectively. At increased levels, however, uric acid may be considered as a marker of oxidative stress due to accumulation of reactive oxygen species. Reprinted with permission from Yao *et al.* (284). (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

provide synergistic protection to the organs against oxidative damage. Therefore, it is more meaningful to evaluate AODS by measuring not only the individual levels but also the total antioxidant status (TAS) in plasma. Using a within-subject, on-off haloperidol treatment design, we have reported reduced plasma TAS in SZ compared to normal controls (291). Using a different method, similar reductions of plasma TAS were also shown in drug-free SZ (3, 259) and chronic SZ (267). On the other hand, plasma total oxidant status was not significantly different between SZ and healthy controls (267). It is likely that the alterations in antioxidant functions may be a consequence of changed symptom severity rather than direct effects of antipsychotic drug treatment. Thus, reduced plasma TAS may have pathophysiological significance in SZ, consistent with AODS alterations reported in association with tardive dyskinesia (35), negative symptoms, neurological signs, poor premorbid function, and computed tomography scan abnormalities (293). Taken together, the observed decreases in plasma TAS as well as individual antioxidants suggest an increased risk for oxidative damage in SZ.

GSH deficits

GSH plays an important role in metabolism, transport, redox signaling (Fig. 2), and cellular protection. The reduced form of GSH is the major nonprotein thiol present in virtually all cells. Its reducing and nucleophilic properties protect cells against destructive effects of ROS and free radicals (161). Using ^{1}H-magnetic resonance spectroscopy (MRS) with double quantum coherence (DQC) filtering and water as an internal standard, Do *et al.* (54) first demonstrated GSH deficits in prefrontal cortex *in vivo* in SZ. Their findings were further supported by reduced GSH levels in cerebrospinal fluid (CSF) of drug-naïve SZ patients, and in plasma of early course or untreated SZ patients (Table 1). Free thiols are also reduced in serum and platelets as well as postmortem caudate in SZ patients (Table 1). Such GSH deficits have been linked to a genetic association between SZ and a GAG trinucleotide repeat polymorphism in the catalytic subunit of the glutamate cysteine ligase, the key enzyme for GSH synthesis (53).

Using ^{1}H-MRS with Point RESolved Spectroscopy sequences and LCModel, Wood *et al.* (276) demonstrated 22% higher levels of GSH in SZ patients than in control subjects. A higher GSH level was more evident in nonresponders to niacin treatment. These authors suggest that GSH is increased in a compensatory manner. However, the mean percent standard deviation of the fit of their GSH was higher than the recommended 20% (or less), making the spectroscopic measurement of GSH less reliable (209). Berger *et al.* (14) failed to detect GSH level using the standard Point RESolved Spectroscopy sequence with TE = 30, suggesting that the GSH measurement by Wood *et al.* (276) might be an artifact. Recent advances in the MRS study of the AODS were reviewed in details by Matsuzawa and Hashimoto in this Forum (158).

Altered levels of scavenging antioxidant enzymes

Among three key scavenging antioxidant enzymes (Fig. 2), SOD has been the most frequently studied. Increased SOD activities have been reported in serum, red blood cells (RBCs), and in frontal cortex and substantia innominata regions of postmortem brains of SZ patients (Table 1) but not by others (233). Neuroleptic-naïve first-episode schizophreniform and schizophrenic patients show both increased SOD activity (129) and decreased SOD activity (84, 177, 212). It is possible that with progression of the illness, the SOD levels rise as a

compensatory response to oxidative stress (177). On the other hand, GSH-Px activity was found to be lower, relative to normal controls, in neuroleptic-treated chronic SZ, and in drug-free female schizophrenic patients (Table 1). In plasma, Zhang *et al.* (307) have reported increased GSH-Px activities in long-term neuroleptic free as well as neuroleptic-naïve SZ patients, whereas Yao *et al.* (288) did not find any significant difference between chronic SZ and normal subjects, but is correlated with psychosis severity. Further, no differences were found in GSH-Px levels from skin fibroblasts of SZ patients and normal controls (307), suggesting that plasma GSH-Px elevation in patients may be state-dependent changes, and not a consequence of course of illness, treatment effects, or neuroleptics.

Examining indvidual enzymes may have limited value for elucidating the role of abnormal AODS in disease processes (217). Since SOD, CAT, and GSH-Px are critical to different stages of free radical metabolism, altered activity of one enzyme without compensatory changes in other enzymes may leave membranes vulnerable to damage. Thus, the differential patterning of the antioxidant enzyme activities may provide important clues to the pathogenetic mechanisms of abnormal free radical metabolism (217). Using a within-subject, repeated measures, on-off haloperidol treatment design, we have further evaluated three critical enzymes of the AODS (SOD, CAT, and GSH-Px) in SZ (288, 290). Among the three major AODS enzymes in erythrocytes and plasma, only RBC-SOD was found significantly higher in drug-free SZ patients than in age- and sex-matched normal volunteers (290). Our findings are consonant with most previous reports of increased SOD activity that have been reported in erythrocytes of drug-free and treated SZ patients.

Nitric oxide signaling

NO is the product of a five-electron oxidation of the amino acid L-arginine by nitric oxide synthase (NOS) (195). There are three isoforms of the NOS family: neuronal (nNOS), inducible (iNOS), and endothelial (eNOS) (70). In human brain, nNOS is primarily responsible for the synthesis of NO (18). Under physiologic conditions, NO and its metabolites react with various thiols (*e.g.*, GSH) to form stable S-nitrosothiols (130). These thiol compounds play an important role in the suppression of NO functions in cellular membranes. Previously, Gegg *et al.* (80) have demonstrated an increase of GSH in astrocytes exposed to NO. Thus, to suppress the NO radical function, the level of cytosolic thiol compounds may be elevated in response to an increased NO production (287). The reaction of NO with free thiols may compete with a substrate such as GSH for decomposition of hydrogen peroxide by GSH peroxidase (Fig. 2).

Changes in cellular expression of brain-associated NOS/nicotinamide adenine dinucleotide phosphate diaphorase have been variable in SZ (2). Increased levels of nNOS were found in cerebellar vermis of SZ (Table 1), but no differences in the expression of NOS in cerebellar granule cells (55). Later, Xing *et al.* (277) demonstrated decreased constitutive NOS activity but normal nNOS protein in the cerebral cortex of SZ patients. In addition, increased levels of nNOS mRNA (9) and reduced hypothalamic nNOS expression (16) were also reported in SZ. Utilizing a sensitive fluorometric assay, Yao *et al.* (287) showed an increased NO production independent of age, brain weight, postmortem interval, sample storage time, alcohol use, or cigarette smoking in postmortem caudate nucleus in SZ. On the other hand, NO metabolites, nitrate and nitrite, were reduced in the CSF samples of SZ patients (213). Peripheral findings have also been inconsistent (Table 1), suggesting that NO and its metabolites may not be of diagnostic values.

Homeostatic imbalance of AODS

GSH redox coupling. The GSH deficiency induced in the animal model has been related to mitochondrial damage (161, 231) and increased free radical insult (5, 185). Moreover, several pathological conditions, including Alzheimer's, Huntington's, and Parkinson's diseases, have been associated with a deficiency of GSH and imbalanced ratio of GSH to oxidized GSH (GSSG) (111, 123). In postmortem caudate region, we (286) have also demonstrated positive correlations between GSH levels and GSH-Px or glutathione reductase (GSH-R) activities in postmortem caudate from control subjects without any psychiatric disorders. Concomitantly, GSH-Px was significantly correlated with GSH-R activities in control subjects (Fig. 5). These positive correlations suggest that a dynamic state regulates the redox coupling under normal conditions. By contrast, lack of such correlations in SZ point to a disturbance of redox coupling mechanisms in the AODS, possibly resulting from a decreased level of GSH as well as age-related decreases of GSSG and GSH-R activities (Fig. 6; for details see subsection Age under section Factors influencing antioxidant status).

A recent integrative review by Do *et al.* (53) posited that redox dysregulation resulting from the convergence between genetic impairments of GSH synthesis and oxidative stress generating environmental insults would lead to hypoactive *N*-methyl-D-aspartate (NMDA) receptors, impairment of fast-spiking parvalbumin GABA interneurons, and a deficit in myelination. Such a defect in GSH redox signaling not only attenuates deaminase (DA) modulation of calcium responses to NMDA (245) but also affects the structural and functional connectivity in the brain, which may contribute to the development of SZ (244). Following an add-on clinical trial with the GSH precursor and antioxidant *N*-acetyl-cysteine, both the negative symptoms (15) and the auditory evoked potential (139) were significantly improved in clinically stable patients with chronic SZ. These findings suggest a novel therapeutic intervention targeting GSH dysregulation in SZ.

Purine catabolism. Mitochondria process most of the cellular oxygen to provide energy that drives almost all metabolic processes, and also are the site of significant free radical production. About 3% of all oxygen consumed is converted to superoxide, and subsequently to hydrogen peroxide (69). Thus, there is an enormous and continuous free-radical burden. Antioxidant systems keep this in check. When the equilibrium between pro-oxidant and antioxidant systems are disturbed in favor of the former, mitochondrial damage can occur. Mitochondrial membranes, similar to neuronal membranes, are vulnerable to lipid peroxidation. Any impairment in mitochondrial oxidative phosphorylation can lead to a broad range of cellular disturbances, including decreased neurotransmission, decreased DNA repair, and, finally, cell death. Cytochrome-c oxidase is a key enzyme in the

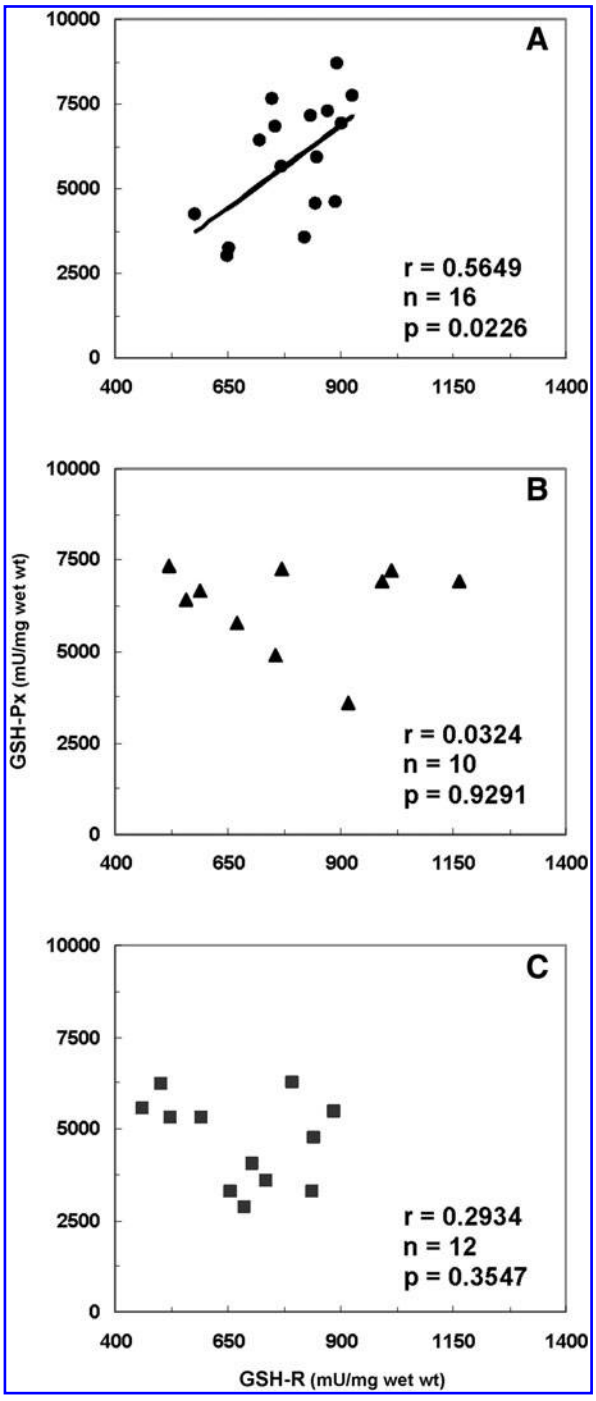

FIG. 5. Correlations of GSH-Px to glutathione reductase (GSH-R) activities in postmortem caudate region. (A) Control subjects without mental disorders, **(B)** control subjects with bipolar and/or depression, and **(C)** patients with SZ. Reprinted with permission from Yao *et al.* (286).

mitochondrial electron transport chain. Decreased activity of this enzyme has been reported in the frontal cortex and caudate nucleus of schizophrenic patients. Several lines of evidence suggest decreased oxidative metabolism in some brain areas in SZ (24, 286, 287), and may be explained in part by mitochondrial dysfunction. We propose that this is secondary to oxidative stress due to decreased antioxidant capacity and/or increased free radical burden.

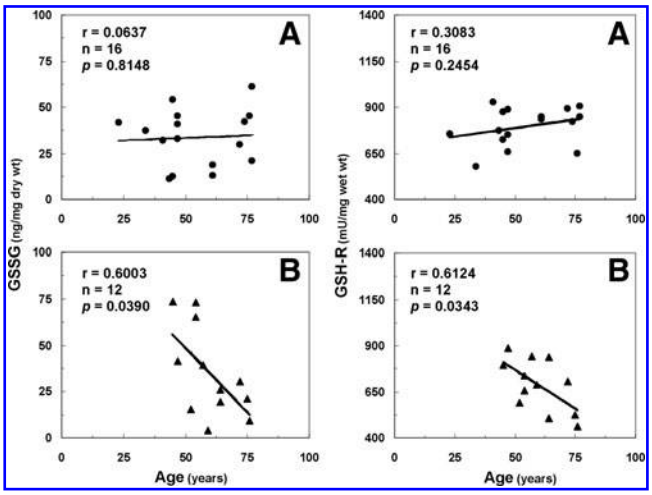

FIG. 6. Correlations of GSSG or GSH-R activities to age in postmortem caudate region. (A) Control subjects without mental disorders, and **(B)** patients with SZ. Reprinted with permission from Yao *et al.* (286).

An early study by Kristal *et al.* (136) indicated that purine catabolism may contribute to mitochondrial antioxidant defense by producing UA. Failure to maintain elevated xanthine and UA occurred contemporaneously with progressive mitochondrial dysfunction. Thus, purine catabolism appears to be a homeostatic response of mitochondria to oxidant stress and may protect against progressive mitochondrial dysfunction in certain disease states (136). In response to oxidative stress, decreased energy charge, or nucleic acid damage, purine metabolism shifts to favor breakdown to xanthine and uric acid.

During the *de novo* synthesis of purine nucleotides, many reactions require a great deal of energy utilizing the hydrolysis of adenosine triphosphate. To provide energy saving for the cell, the purine bases can be reutilized *via* salvage pathways (41) by converting adenine, guanine, or hypoxanthine (Hx) to AMP, GMP, or IMP, respectively (shown dotted arrow in Fig. 3). The unsalvaged Hx is then converted to xanthine (Xan), which is further converted to UA by xanthine oxidase. In humans, UA is the final product of purine catabolism (142), which has been implicated as a risk factor and cause of numerous pathological conditions (see below).

Recently, we have evaluated the purine pathway by quantitative determinations of six major purine metabolites consisting of xanthosine (Xant), Xan, Hx, guanine (G), guanosine (Gr), and UA (284). During the purine degradations, both conversions from Gr to G and from Xant to Xan are readily reversible (Fig. 3). Altered ratios of product to precursor, that is, significantly decreased ratios of G/Gr, UA/Gr, and UA/Xant, and the increased ratio of Xant/G, suggested a shift favorable to the Xant formation (approximately twofold increase) in the first-episode neuroleptic-naïve patients with schizophrenia (FENNS). Consequently, the potential for steady formation of UA from purines was reduced at first testing of the patients, which is shown in the red arrow of Figure 3. In addition, there are tightly correlated precursor and product relationships within purine pathways; although some of these correlations persist across disease or medication status, others appear to be lost among FENNS. Taken together,

these results suggest that the potential for steady formation of antioxidant UA from purine catabolism is altered early in the course of SZ and may be independent of treatment effects.

Increased lipid peroxidation and protein modifications

Lipid peroxidation. Changes in antioxidant defense system such as decreased plasma TAS do not necessarily reflect an increased oxidative stress and subsequent membrane lipid damage. While evidence of peroxidative damage is limited to SZ patients, the findings have been consistent. Increased blood levels of malondialdehyde (MDA) were found in SZ patients (Table 1). A similar increase of lipid peroxides was also demonstrated in CSF samples (146) and platelets (50) of SZ patients. In addition, elevated plasma lipid peroxides were also shown at the onset of psychosis in never-medicated, first-episode SZ patients (153), suggesting the presence of oxidative stress at very early in the course of illness, and independent of treatment. Increased concentrations of pentane and ethane, which are other markers of lipid peroxidation, have also been reported in SZ relative to normal controls (Table 1). By contrast, findings from Scottish SZ Research Group (230) and Skinner *et al.* (235) do not support the view that increased lipid peroxidation is associated with the SZ *per se*.

Although the classical determination of MDA by complexion with thiobarbituric acid reactive substances is widely used for assaying lipid peroxides, clinical application is somewhat limited because of concerns relating to analytical specificity, sensitivity, reproducibility, recovery, sample instability, and drug interference (109). One alternative approach is to determine isoprostanes, which are prostaglandin isomers resulting from free radical insult of arachidonic acid (AA) *in situ* on membrane phospholipids (175). Isoprostanes are chemically stable end-products of lipid peroxidation and are excreted in urine (8). The increased plasma MDA levels were supported by a significantly increased excretion of isoprostanes in urine of the same SZ patient individuals as compared to control subjects (52).

Protein modifications. There are high levels of free radicals that are formed by the mitochondrial respiratory chain, with subsequent damage to mitochondrial proteins, DNA, and lipids (182). Protein oxidation is identified as carbonyl formation resulting from ROS, and 3-nitrotyrosine as a marker of reactive nitrogen species. Increased oxidative/nitrative modifications have been demonstrated in both plasma and platelet proteins of SZ patients (Table 1). By application of immunohistochemistry determining 4-hydroxynonenal protein adducts, Wang *et al.* (269) have recently shown that levels of 4-hydroxynonenal (a major product of lipid proxidation) were also significantly increased in the postmortem anterior cingulate brain from SZ patients. Recent advances in proteomic studies have provided considerable evidence further supporting a role of oxidative stress in SZ (156).

Factors influencing antioxidant status

Age. Previous studies have linked aging process to oxidative injury (58, 73). The balance between free radical production and antioxidant defense system is an important mediator of the mechanism of aging (92). In general, the rate of oxidative damage by free radicals to membranes provides us an index to determine life span (91, 171, 232). Previously, we have reported that reduction of plasma antioxidant proteins appears to be age related in patients with chronic SZ (292). Contrary to normal control subjects, there was an inverse correlation between plasma albumin and age in SZ. On the other hand, plasma total bilirubin levels were positively correlated with age in normal control subjects, but not in SZ patients. Such age-related correlations were not found in the FENNS and age-matched normal controls (219), perhaps resulting from a narrow range of age (mean age, 28 years; range, 18–40 years) in the FENNS group as compared to the previously reported patients with chronic SZ (mean age, 35 years; range, 18–55 years).

Recently, in the caudate region of postmortem brains, we (286) have further shown that both GSSG and GSH-R levels were significantly and inversely correlated to age of SZ patients, but not control subjects (Fig. 6). However, the plasma AODS enzyme activities were not significantly correlated with subject age, age of onset of illness, or the duration of illness (288, 290). It is likely that decreased levels of GSH result from a decrease of GSH-R in the brain with aging, suggesting an increased susceptibility to oxidative damage with accelerated aging. In addition, several lines of evidence indicate accelerated aging processes in SZ (132). Certain biomarkers of aging, including telomere functioning (68, 121, 205), deficient insulin-like growth factor-1 levels (264), and increased interleukin (IL)-6 levels (206, 282), were also abnormal in SZ patients. Taken together, age appears to be an important factor modifying AODS in SZ.

Antipsychotic drugs. Applying the controlled discontinuation of haloperidol in patients with chronic SZ, we have previously examined the antipsychotic effects on plasma antioxidant status. Neither individual antioxidant levels nor total antioxidant status were significantly affected by antipsychotic treatment (194, 267, 289, 291, 292). More importantly, the altered AODS were observed independent of treatment since patients were antipsychotic drug-naïve at entry into the study (194, 212, 219, 267). Although decrease of plasma uric acid levels were observed in patients after haloperidol withdrawal (289), it is unlikely that the decreased uric acid levels in patients with chronic SZ are due to the antipsychotic effects since the haloperidol treatment was associated with increased uric acid levels within SZ patients. Similarly, neither increased serum nitric oxide levels (253) nor increased lipid peroxidation (75, 193, 302) in SZ patients were affected by antipsychotic treatment. A recent study by Lee and Kim (140) further indicated that plasma NO levels in SZ patients were significantly lower than in normal controls both before and after 6-week treatment with risperidone.

On the other hand, several other studies have shown that blood levels of TAS (3), SOD (43, 306), MDA (3), IL-2 (306), and thioredoxin (301) may be regulated by antipsychotic treatment in SZ patients. Miljevic *et al.* suggested that atypical antipsychotic drugs (*e.g.*, clozapine)-induced metabolic syndrome may be mediated through the oxidative stress mechanisms (169).

In postmortem studies, it is possible that alterations in the GSH redox state are attributable to the long-term treatment with antipsychotic drugs that SZ patients likely received. In our previous study (286), all patients were on antipsychotic

medications at the time of death. No significant differences, however, were shown in the caudate mercaptans between control subjects with or without nonschizophrenic psychiatric disorders. Grima *et al.* (86) have proposed that GSH deficit in SZ may be associated with dopamine-induced oxidative stress. Antipsychotic drugs are known to block DA receptors and, consequently, may result in increased levels of GSH. Therefore, the GSH deficit is unlikely due to antipsychotic effects, because GSH levels may be lower in SZ patients in the absence of antipsychotic treatment.

Data on the effect of antipsychotic drugs on molecular markers are complicated by the lack of complete database on the dose and duration of different antipsychotic drugs taken by the patients. Data from animal model studies have indicated that antipsychotic drugs may have differential effects (time and dose dependent) on molecules in redox signaling (203).

Diet. Diet, caloric intake, and alcohol can affect both the antioxidant system and the production of free radicals (196). Malnutrition can cause low plasma albumin levels (170). In our previous studies examining antioxidant capacity in plasma (289–292, 297), SZ patients were all hospitalized and maintained on a controlled and balanced diet without alcohol consumption. Subsequent studies in FENNS (219), all participants including controls were recruited from the general population, without a controlled diet. In general, patients were not undernourished as indicated by the normal range of body mass indices. Systematically examining the associations between diet, sociodemographic, and physical characteristics in community-dwelling SZ patients, Strassnig *et al.* (246) concluded that SZ patients do not make dietary choices different from those of people in the general population. Thus, dietary factors may not have predominant confounding effects on plasma antioxidant capacity.

Although diet has profound effect on the developing brain, the mature brain is more resistant to undernutrition (82). It is unlikely that diet alone accounts for the findings of AODS defects in SZ patient groups from different countries and different continents.

Cigarette smoke. Cigarette smoke contains many pro-oxidants in both the gas and tar phases, and may contribute directly to oxidative stress and decreases in antioxidants (37, 210). One of the major compounds in the gas phase of tobacco smoke is nitric oxide. It has been suggested that nitric oxide reacts with smoke olefins to form carbon-centered radicals (210). The tar phase consists of a semiquinone radical that promotes hydrogen peroxide formation. Moreover, tobacco smoke may increase free radical formation by activating neutrophils.

On the other hand, several *in vivo* studies have shown antioxidant properties of nicotine (67, 143), which might explain the protective effects of smoking against the development of Parkinson's disease (239). Cigarette smoking by SZ patients exceeds the rates in the general population by 2–3-folds (102, 145, 189). Some investigators have suggested that cigarette smoking in schizophrenic patients may be a method of self-treatment (189) or smoking may serve as a behavioral filler (102), or there may be an underlying neurobiological cause (243). Further, smoking may help to offset the sedative or other adverse effects of psychotropic medications. It has been shown that smoking decreases the blood levels of many psychoactive agents by activating hepatic microsomal enzyme systems, thereby increasing their metabolism (102), and may help overcome the dopaminergic blockade and associated medication side effects, including akathisia, drowsiness, dystonia, and Parkinsonism (145). Some, or all, of these factors may underlie the high rates of smoking in schizophrenic patients (218).

Previously, we have shown that cigarette smoking can significantly reduce the levels of plasma bilirubin (292) but not of albumin (219, 292) and uric acid (219, 289). Although bilirubin is a more efficient antioxidant than albumin, the overall contribution of plasma TAS from bilirubin is only $<5\%$ as compared to that of $>70\%$ from albumin and uric acid (169, 271). Moreover, plasma TAS was not correlated with levels of plasma cotinine (291), which is the major metabolite of nicotine. Recent findings from Ustundag *et al.* (259) also showed significantly lower levels of plasma TAS in medication-free SZ patients independent of smoking habits. Similarly, levels of plasma MDA were significantly higher in chronic SZ patients than in age-, gender-, and smoking-matched healthy control subjects (302). Approximately 68%–70% of subjects were smokers in both patient and control groups. In addition, serum thioredoxin levels were not significantly different between smokers and nonsmokers (301). Taken together, cigarette smoking alone does not appear to be a confounding factor in altering AODS in SZ patients, although increased oxidative stress may be associated more with the smokers than the nonsmokers (230, 259, 304).

Oxidative Stress, Membrane Dynamics, Immune Response, and Neurotransmission

Much of the research focus in SZ has been on neurotransmitter systems. Although the role of dopamine in the pathophysiology of SZ remains preeminent, recent findings suggest instead that multiple neurotransmitter systems may be involved. Whether these are primary or secondary to other pathological processes, such as oxidative stress and membrane dysfunction, will need to be determined in future studies. It is important to recognize, however, that alterations in the metabolism of several neurotransmitter systems can both contribute to, and be modified by oxidative stress (or membrane dysfunction).

Altered phospholipids and PUFAs

Membrane PUFAs highly susceptible to free radical insult. Lipids account for $\sim 50\%$ of the brain's dry weight. Phospholipids in particular constitute 50%–70% of the makeup of brain lipids (251), which contain high levels of PUFAs, most notably AA (n-6) and docosahexaenoic acid (DHA; n-3). PUFAs are highly susceptible to free radical insult and autooxidation to form peroxyradicals and lipid peroxide intermediates, the existence of which within cell membranes (Fig. 7) results in unstable membrane structure, altered membrane fluidity and permeability, and impaired signal transduction (62). Hydroperoxides can further decompose to other toxic species (aldehydes, including malonyldialdehyde), which can damage adjacent cells, membrane-bound enzymes, and receptors, cause cross-linking between various types of molecules, and result in membrane breakdown, cytotoxicity, mutagenicity, and enzyme modification (33, 34, 62). Aldehydes can react with lipids and proteins forming lipofuscin,

which accumulates in neuronal cells, particularly in regions of active free radical metabolism.

Thus, the unchecked effects of free radicals can result in cellular dysfunction, loss of membrane integrity, and even cell death. The brain, which is rich in PUFAs, is particularly vulnerable to free-radical-mediated damage.

Abnormal phospholipid metabolism. There are a variety of findings indicative of defects in phospholipid metabolism and cell signaling in patients with chronic SZ as well as in first-episode neuroleptic naïve patients with SZ (59, 151, 236). These findings include (i) decreased PUFAs and altered phospholipids in plasma (98, 115), RBC (7, 83, 118, 128, 187, 199, 220, 296), platelets (77), skin fibroblasts (150, 152), and postmortem brain tissues (98, 160, 227, 285); (ii) increased levels of DHA in CSF (117); (iii) increased turnover of inositol phospholipids (48, 64, 298) and production of second messengers (116, 295); (iv) decreased incorporation of AA in platelets (48, 295); and (v) increased lipid peroxidation in plasma (128, 153), CSF (146, 193) and platelets (50).

Support for central membrane dysregulation in SZ is also derived by *in vivo* ^{31}P MRS techniques, which assay the relative concentrations of phospholipid precursors and breakdown products, phosphmonoesters, and phosphodiesters, respectively (Fig. 8). Using this methodology, Pettegrew *et al.* (200, 201) demonstrated a significant reduction of phosphmonoester and significantly increased levels of phosphodiester in frontal cortices of FENNS as compared to controls. In addition, an increased adenosine triphosphate and decreased inorganic orthophosphate levels were also found in the frontal cortex. Pettegrew and colleagues (201) suggested that changes in membrane phospholipids might be related to molecular changes that precede the onset of clinical symptoms and brain structural changes in SZ, whereas changes in high-energy phosphate metabolism may be state dependent. Other groups (47, 74, 242, 273) also reported similar findings in membrane phospholipid perturbations in both acutely and chronically ill patients. Also, based on ^{31}P MRS findings, Keshavan *et al.* (126, 127) suggested a possible familial basis for membrane phospholipid changes in SZ. Yao *et al.* (294) have shown that ^{31}P MRS and peripheral indices of phospholipid metabolism may be correlated. Given the obvious need for central measures of brain structure and function, these techniques may prove highly valuable in the further explication of the specific phospholipid and fatty acid abnormalities evident in SZ (158).

Taken collectively, there is ample evidence for the existence of membrane phospholipid and fatty acid defects in early course and chronic SZ. It is thus reasonable to hypothesize that increased oxidative stress may be one of the mechanisms responsible for reduction of membrane PUFAs.

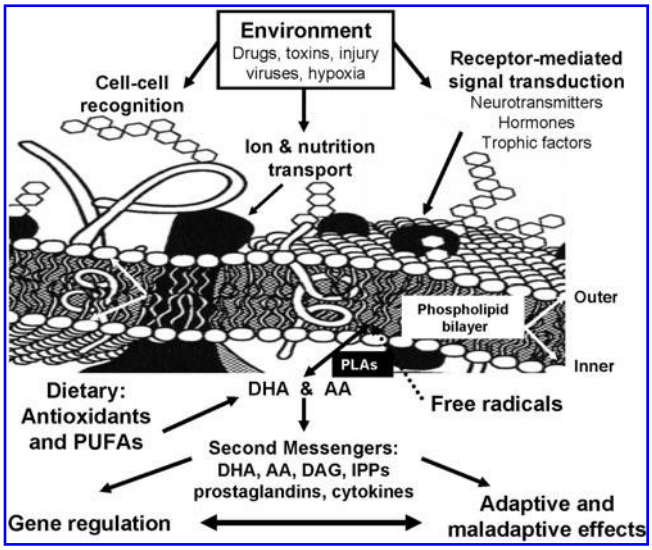

FIG. 7. Schematic membrane structure illustrating the key components and their functional role in cell–cell interaction, interaction with environmental factors, and receptor-mediated signal transduction. Membrane model shows the phospholipid bilayer with embedded in it the receptors for neurotransmitters, physiological mediators and growth factors, transporters for ions and nutritional ingredients, and signal transduction machinery. Phospholipid bilayer is made up of four major phospholipids, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), and phosphatidylserine (PS), which are asymmetrically localized, that is, PC predominantly on outer lipid layer and PE, PI, and PS on inner lipid layer. PE, PI, and PS are highly enriched in arachidonic acid (AA) and docosahexaenoic acid (DHA), which are released by receptor-mediated phospholipases (PLAs). AA and DHA, and their metabolic products, diacylglycerol (DAG), inositol polyphosphates (IPPs), and prostaglandins work as second messengers and physiological mediators, including gene modulation, and thus lead to adaptive and maladaptive cellular changes. Reprinted with permission from Mahadik and Yao (151).

PUFAs, immune dysfunction, and oxidative stress

PUFAs and immune response. Both n-6 and n-3 PUFA are involved in the regulation of inflammatory response system. The n-6 PUFAs, particularly AA, have the pro-inflammatory features, since AA is the precursor of pro-inflammatory eicosanoids, prostaglandin E_2, and leukotriene B_4 and increase production of IL-1, tumor necrosis factor, and IL-6 (93, 240, 254). On the other hand, the n-3 PUFAs eicosapentaenoic acid (EPA) and DHA suppress the production of AA-derived eicosanoids, thus having anti-inflammatory and immunosuppressive effects (28, 166). Previous studies on n-3 PUFA-enriched diets (*e.g.*, fish oil) have shown partial replacement of AA by EPA in inflammatory cell membranes and significantly reduce the *ex vivo* production of pro-inflammatory cytokines (28, 61, 63, 108, 166, 240). Therefore, an imbalance of n-6/n-3 PUFAs may result in an increased production of pro-inflammatory cytokines.

Inflammatory response and ROS production. The inflammatory response is intimately connected with oxidative stress *via* free radical generation (57). During inflammatory processes, infiltrating cells can produce large amounts of ROS. In addition being cytotoxic, these ROS also act as important mediators regulating various cellular and immunological processes. Under physiologically relevant concentration, hydrogen peroxide was shown to either increase the production of T-cell growth factor (223) or induce the gene expression of IL-2 (148) and IL-6 (113). The enhancement of IL-2 production was associated with a decrease in the intracellular GSH level (148) and was reversed by the addition of exogenous GSH

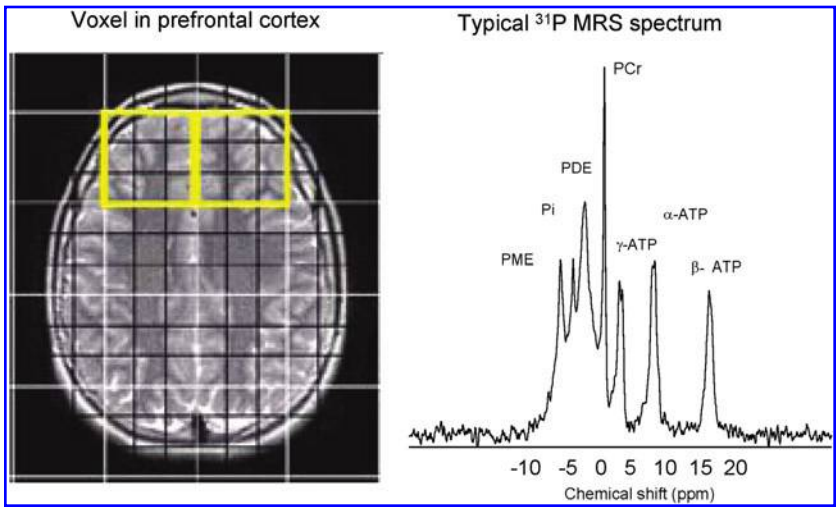

FIG. 8. A typical *in vivo* ^{31}P magnetic resonance spectrum from the prefrontal region of a healthy subject. The *left panel* shows the voxel placement for the spectral acquisition, and the *right panel* shows the spectrum. The x axis represents the frequency in parts per million (ppm). ATP, adenosine triphosphate; PCr, phosphocreatine; PDE, phosphodiester; Pi, inorganic phosphate; PME, phosphomonoesters. (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

(222). Hehner *et al.* (95) have further demonstrated enhancement of T cell receptor signaling by a shift in the intracellular GSH redox state. Above findings thus suggest that the intact immune system requires a delicate balance between antioxidant and prooxidant status (56).

In SZ, the unspecific, innate immune system appears to be overactivated as evident by an increase of monocytes (272) and gamma/delta cells (180), resulting in an increased release of IL-6 (76, 261). By contrast, there is a decreased *in vitro* production of IL-2 (17, 32, 265) as well as decreased production of interferon-γ (6, 224, 272), which suggests that the Th-1 system is underactivated in SZ. Since the Th2 system can produce IL-6, Müller *et al.* (178) suggested an imbalance of adaptive immune system with a shift to the Th2-like immune reactivity in a subgroup of patients with SZ. This subgroup is further characterized by more pronounced negative symptoms and poor outcome (228).

However, data published so far have been inconsistent, which may be the result of differences in assay methodology, sample size, sample handling, diagnostic criteria, and comparison groups (282). In addition, several confounding factors, including age, gender, ethnic background, smoking, alcohol, substance abuse, and antipsychotic treatment may also explain these discrepancies (10). In a recent meta-analysis of 62 cross-sectional studies involving 2298 SZ patients and 1858 healthy volunteers, Potvin *et al.* (206) concluded that SZ patients have increased levels of *in vivo* IL-1 receptor antagonist, soluble IL-2 receptor, and IL-6, and decreased levels of *in vitro* IL-2, establishing an inflammatory syndrome in SZ.

Oxidative stress, immune dysfunction, and membrane defects. A number of putative mechanisms have been identified to explain the decreased PUFA levels in SZ (299), notably increased breakdown of phospholipids and decreased incorporation of AA. Both increased oxidative stress and altered immune function may play a role in an induction of phospholipase activities, for example, phospholipase A_2 (PLA_2) responsible for breakdown of membrane phospholipids (Fig. 9). This association is particularly relevant in relation to phospholipids/PUFA, because AA can be converted to a variety of biologically active eicosanoids that serve as potent messengers in regulating the inflammatory response. Indirect evidence for a dysregulated inflammatory response in SZ stems from the observation of a negative association between SZ and rheumatoid arthritis (163, 258, 266) and decreased prostaglandin-dependent niacin skin-flushing in SZ (99, 164, 165).

Direct evidence of immune changes in SZ have also come to light, particularly in the activities of several cytokines (*e.g.*, IL-2 and IL-6) known to be abnormal in autoimmune dysfunction (78, 282, 306). Given the diverse physiological function of AA, the specific behavioral symptomatology of SZ is related mostly to the effect of AA changes that regulate neurodevelopment, neurotransmitter homeostasis, second messenger signaling, and neuromodulatory activity in SZ. Hence, in the current conceptualization, AA may be at a nexus point in the cascade leading to the syndrome of SZ (Fig. 9), and represents a common biochemical pathway leading to the highly heterogeneous symptomatology and course of SZ (236).

Neurotransmitters as contributors to free radical burden

Previous studies have shown that dopamine metabolism yields free radicals under normal physiological conditions (40). A number of DA metabolic pathways exist that lead to the generation of hydroxyl radicals (Fig. 10). DA is susceptible to autoxidation when the antioxidant defense system is weak (300). Moreover, the progressive loss of DA triggers an increase in DA turnover in the remaining neurons and facilitates the accumulation of toxic byproducts of DA metabolism. Interestingly, DA-induced toxicity is also mediated through DA actions on the NMDA glutamate receptors (14, 26, 167). There is accumulating evidence that NMDA-mediated excitotoxicity involves free radicals such as superoxide and nitric oxide (42, 197). In fact, antioxidants (*e.g.*, ascorbate and α-tocopherol) protect neurons against glutamate neurotoxicity (39, 149).

Other neurotransmitters, particularly glutamate, can induce other metabolic processes that increase free radical production. Activation of NMDA by glutamate stimulates PLA_2 activity to release AA to act as a second messenger, which in turn can lead to the formation of free radicals (106). Decreased availability of AA, due either to increased PLA_2 activity or lipid peroxidation, can lead to impaired glutamatergic neurotransmission, which has been proposed as a

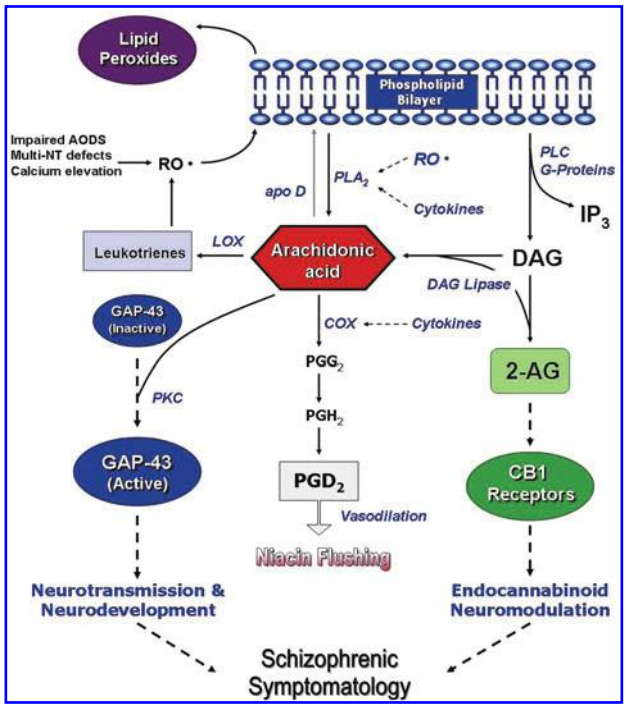

FIG. 9. A putative model integrating lipid peroxidation, phospholipids turnover, AA signaling, and SZ symptomatology. As shown, several possible mechanisms can lead to increased phospholipid breakdown and AA release, including decreased AA incorporation and increased phospholipase activities (PLA_2 and PLC), possibly resulting from increased oxidative stress and cytokine release. The resulting changes in AA level could then affect more downstream processes, including neurodevelopment *via* growth-associated protein (GAP)-43, neurotransmitter homeostasis, phosphatidylinositol signaling, and neuromodulatory actions of endocannabinoids. It is proposed that the specific behavioral symptomatology of SZ is related mostly to the effect of AA changes on the neurochemistry of deaminase, glutamate release, and circulating levels of the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG). In addition, alterations in AA may also affect the inflammatory response, which can then affect PLA_2 release *via* cytokines, further exacerbating phospholipid turnover and AA release. Hence, in the current conceptualization, AA is at a nexus point in the cascade leading to the syndrome of SZ, and represents a common biochemical pathway leading to the highly heterogeneous symptomatology of psychosis. Reprinted with permission from Skosnik and Yao (236). (To see this illustration in color the reader is referred to the web version of this article at www.liebertonline.com/ars).

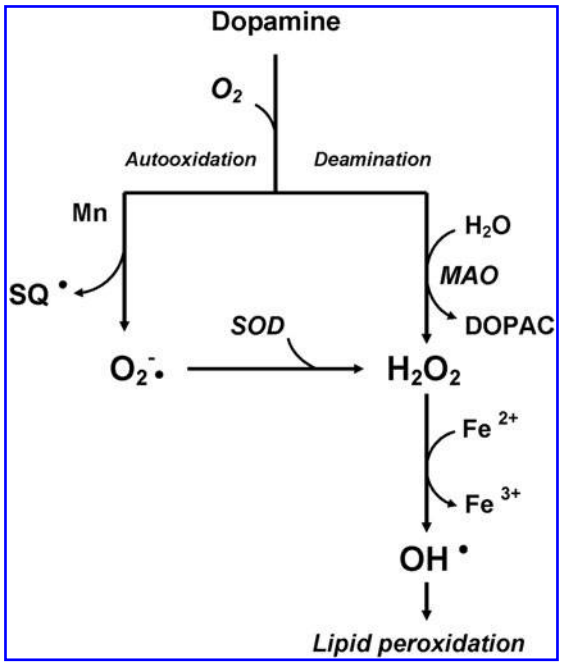

FIG. 10. Autooxidation and oxidative deamination of dopamine. In the presence of Mn, the auto-oxidation of dopamine produces semiquinones (SQ) and superoxide radicals ($O_2^{-}\bullet$), as well as H_2O_2, which is readily converted to OH• in the presence of Fe^{2+}. On the other hand, the enzymatic oxidation of dopamine by monoamine oxidase (MAO) can also produce H_2O_2 and, subsequently, generate the toxic OH•.

pathogenetic mechanism in SZ (29, 190). A dopamine-glutamate imbalance has also been implicated in SZ (30). Neuroleptic drugs that block dopamine receptors may also enhance the glutamatergic neurotransmission.

Recently, using a targeted electrochemistry-based metabolomics platform, we have compared metabolic signatures consisting of 13 plasma tryptophan-metabolites simultaneously (Fig. 11) between FENNS patients and healthy controls, and between FENNS at baseline (BL) and 4 weeks after antipsychotic treatment (283). It was noted that conversion of serotonin to *N*-acetylserotonin by serotonin *N*-acetyltransferase may be upregulated in FENNS patients, possibly related to the observed alteration in tryptophan and 5-hydroxyindoleacetic acid correlation. Considering *N*-acetylserotonin as a potent antioxidant (79, 274), such increases in *N*-acetylserotonin might be a compensatory response to increased oxidative stress, implicated in the pathogenesis of SZ.

Clinical Implications

Since the pathophysiology in SZ still remains unclear, understanding the clinical implications of oxidative stress and membrane deficits is also limited. Many of the previously unexplained clinical characteristics of SZ, including high pain tolerance, differences in severity and prognosis across different countries (due to dietary variations), the inverse relationship between SZ and some inflammatory disorders, and the remission of symptoms that occur during high fever, may be explained by membrane phospholipid abnormalities (100, 236). However, to directly link the observed AODS defects with SZ pathogenesis, it is necessary to establish a relationship between the traditional positive/negative symptoms of the disease and the noted aberrations in AODS. While preliminary evidence in this regard has been admittedly correlative, such associations between altered AODS indices and clinical symptoms may provide the building blocks for determining causal relationships and developing novel treatment options.

To date, several laboratories have demonstrated associations between AODS enzymes and symptom severity. In platelets, Buckman *et al.* (25) found that GSH-Px activity was inversely correlated with computed tomographic scan measures of brain atrophy in patients with chronic SZ, specifically nonparanoid SZ with a predominance of negative symptoms. Positive symptoms, however, have been correlated with SOD

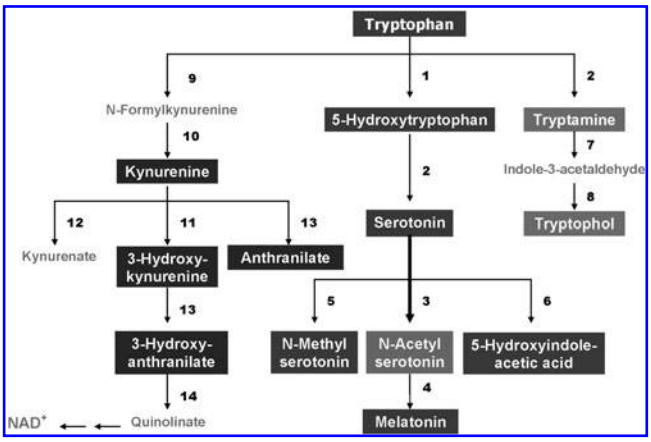

FIG. 11. Tryptophan metabolic pathways. The *bolded arrow* indicates that pathway may be upregulated in first-episode neuroleptic-naïve patients with SZ. **1**, tryptophan hydroxylase; **2**, aromatic L-amino acid decarboxylase; **3**, serotonin *N*-acetyltransferase; **4**, 5-hydroxyindole-O-methyltransferase; **5**, serotonin *N*-methyltransferase; **6**, monoamine oxidase and aldehyde dehydrogenase; **7**, monoamine oxidase; **8**, alcohol dehydrogenase; **9**, tryptophan 2,3-dioxygenase; **10**, formamidase; **11**, kynurenine 3-monooxygenase; **12**, kynurenine transaminase; **13**, kynureninase; **14**, 3-hydroxyanthranilate oxigenase. Reprinted with permission from Yao *et al.* (283).

activity (129). Decreased SOD activity is associated with impaired premorbid school functioning (177) and tardive dyskinesia (278).

Systematic evaluation of relations between three key scavenging antioxidant enzymes and various psychosis rating scales in drug-free schizophrenic patient groups, both RBC and plasma GSH-Px, was found to be significantly and positively correlated to the Bunney-Hamburg psychosis ratings (BHPR) (288, 293). Such a correlation was present in patients both on and off haloperidol treatment. On the other hand, RBC-SOD activities were inversely and significantly correlated with the BHPR or the Scale for the Assessment of Negative Symptoms (SANS) scores. Later, Zhang *et al.* (305) also demonstrated that blood SOD levels were positively correlated with the Brief Psychiatric Rating Scale (BPRS) and Scale for the Assessment of Positive Symptoms (SAPS) total scores in SZ patients.

In addition, significant inverse correlations between plasma TAS and the SANS were demonstrated in drug-free schizophrenic patients (259, 291). A similar inverse correlation between plasma uric acid and BHPR scale was also demonstrated in schizophrenic patients both on and off haloperidol treatment (289). Moreover, plasma bilirubin levels were significantly lower in the negative subgroup of the SZ patient group (194), whereas SZ patients with higher levels of plasma bilirubin showed higher scores on the positive subscales of the Positive and Negative Syndrome Scale (172).

Recently, Zhang *et al.* (303) have demonstrated that plasma MDA levels were positively correlated with Abnormal Involuntary Movement Scale total score and the SANS in SZ patients with tardive dyskinesia. In addition, serum thioredoxin was significantly correlated with SAPS (301), and plasma NO levels were negatively correlated with SANS in SZ patients (184). Taken together, above findings suggest that alterations in AODS enzymes and antioxidant status may be a related to changed symptom severity rather than being direct effects of antipsychotic drug treatment, and further suggest the possibility of therapeutic approaches using currently available treatments (215).

Summary and Future Directions

SZ is a major mental disorder without a clearly identified pathophysiology. A number of putative mechanisms have been proposed to explain the etiopathogenesis and illness presentation of SZ, including abnormal neuronal development, impaired neurotransmission, viral infections *in utero*, autoimmune dysfunction, and many others. Extensive, though fragmentary, findings from neurochemical and neuroendocrine studies of SZ have not provided conclusive evidence for any specific etiologic theory of SZ, perhaps due to etiopathogenetic heterogeneity. However, there exists a point of convergence for many of these theoretical models, one that occurs at the level of the neuronal membrane, which is the site of neurotransmitter receptors, ion channels, signal transduction, and drug effects. Membrane deficits, specifically free radical-mediated, can significantly alter a broad range of membrane functions. There is abundant evidence that alterations in key neurotransmitters can both be modified by and contribute to oxidative stress and membrane dysfunction, suggesting a link among oxidative stress, membrane dysfunction, and multineurotransmitter pathologies in SZ (59, 236, 282).

Research into the pathophysiology of SZ is replete with findings across a large variety of discrete biological systems that in many instances are replicable. It must be assumed that

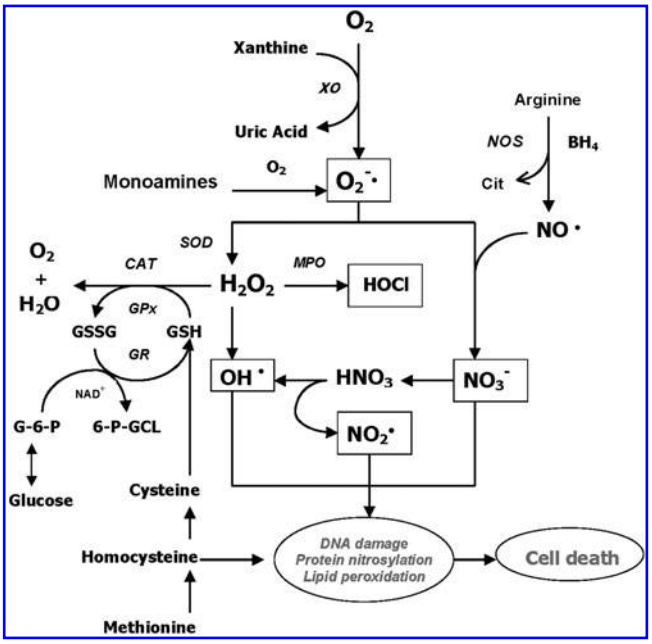

FIG. 12. Antioxidant defense system involving multiple biochemical pathways. It is surmised that some, or all, of these alterations in purine catabolism, neurotransmission, glutathione redox coupling, glucose phosphorylation, one-carbon metabolism, and nitric oxide synthase activation may contribute to oxidative stress and membrane dysfunction in SZ. Reprinted with permission from Yao and Reddy (281).

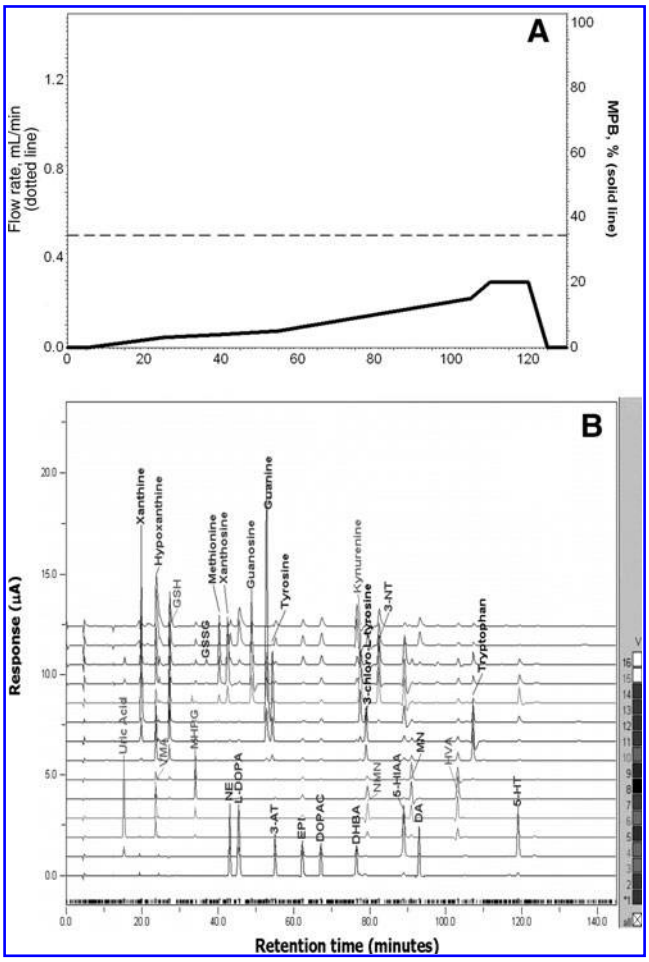

FIG. 13. Separation of low-molecular-weight, redox-active compounds by high-pressure liquid chromatography coupled with a Coulometric Multielectrode Array System. (A) Flow rate and mobile phase gradient profile; **(B)** 16-channel chromatograms obtained by separation of standard mixture in a single column (ESA Meta-250, 5 µm ODS, 250 × 4.6 mm ID) under a 150-min gradient elution that ranged from 0% to 20% MPB with a fixed flow rate of 0.5 ml/min **(A)**. The temperature of both cells and column was maintained at 25°C. The Coulometric Multielectrode Array System was set to have increments from 0 to 900 mV in 60 mV steps. Reprinted with permission from Yao and Reddy (281).

these findings in multiple systems in the same disorder are likely linked to each other in meaningful ways, and explicating such relationships will permit a more accurate understanding of the dynamics of the underlying pathology. In this review, defects in the antioxidant system, membrane composition, immune response, and neurotransmission were reported in SZ patients. A recent study by Kale *et al.* (118) reported reduced levels of folic acid and vitamin B_{12}, and increased levels of homocysteine and cortical in never-medicated SZ patients, further indicating an altered one-carbon metabolism in SZ. Conceptually, these abnormalities can be linked (Fig. 12) but until now there has been no practical way of simultaneously examining these discrete, but interrelated, large systems. Therefore, future studies should focus to identify candidate pathological process(es) that account for the complex constellation of clinical and biological features in SZ.

Novel, powerful, and rapid multidimensional separation and characterization methods, for example, high-pressure liquid chromatography coupled with a 16-channel coulometric multielectrode array system (Fig. 13), can lead to revolutionary changes in our understanding at the molecular level (114, 135, 225, 280, 281). The resolving power of these methods is superior to one-dimensional approaches, enabling the comprehensive metabolic analyses particularly in the targeted biochemical pathways. A metabolomic analytic approach has the potential to yield valuable insights into the likely complex pathophysiological mechanisms that affect multiple metabolic pathways (283, 284), and thereby offer multiple windows of therapeutic opportunities. Examples of such interventions include dietary supplementation with a combination of n-3 PUFAs and antioxidants for treatment of SZ patients, particularly in the early stages of illness (59, 155), and in reducing the risk of progression to psychotic disorder in patients with prodromal symptoms (4), and the use of *N*-acetyl cysteine, a GSH precursor and antioxidant, in treatment of negative symptoms of SZ. Clearly, the redox signaling hypothesis of SZ offers unique ways of thinking out of the box to develop novel, hypothesis-driven interventions to treat this highly disabling disease.

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Abbreviations Used

2-AG = 2-arachidonoyl glycerol
AA = arachidonic acid
AODS = antioxidant defense system
ATP = adenosine triphosphate
BHPR = Bunney-Hamburg psychosis ratings
CAT = catalase
CSF = cerebrospinal fluid
DA = deaminase
DAG = diacylglycerol
DHA = docosahexaenoic acid
eNOS = endothelial nitric oxide synthase
FENNS = first-episode neuroleptic-naïve patient with schizophrenia
GAP = growth-associated protein
GSH = glutathione
GSH-Px = glutathione peroxidase
GSH-R = glutathione reductase
GSSG = oxidized glutathione
H_2O_2 = hydrogen peroxide
Hx = hypoxanthine
IL = interleukin
iNOS = inducible nitric oxide synthase
IPPs = inositol polyphosphates
MAO = monoamine oxidase
MDA = malondialdehyde
MRS = magnetic resonance spectroscopy
NMDA = *N*-methyl-D-aspartate
nNOS = neuronal nitric oxide synthase
NO = nitric oxide
NOS = nitric oxide synthase
$OH^{\bullet}$ = hydroxyl radical
PC = phosphatidylcholine
PCr = phosphocreatine
PDEs = phosphodiesters
PE = phosphatidylethanolamine
Pi = inorganic phosphate
PI = phosphatidylinositol
PLA_2 = phospholipase A_2
PLC = phosphorlipase C
PMEs = phosphmonoesters
PS = phosphatidylserine
PUFAs = polyunsaturated fatty acids
RBC = red blood cell
ROS = reactive oxygen species
SANS = Scale for the Assessment of Negative Symptoms
SOD = superoxide dismutase
SZ = schizophrenia
TAS = total antioxidant status
UA = uric acid
Xan = xanthine
Xant = xanthosine
XO = xanthine oxidase

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