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Free radical pathology in schizophrenia: a review

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Summary There is evidence that free radicals are involved in membrane pathology, and may play a role in schizophrenia. Free radicals are reactive chemical species generated during normal metabolic processes, and, in excess, can damage lipids, proteins, and DNA. Regions of high oxygen consumption, lipid content, and transition metals are at particular risk. Hence, neuronal membranes are uniquely vulnerable to radical-mediated damage. Elaborate antioxidant defense systems exist to protect against oxidative stress. In schizophrenia there is evidence for dysregulation of free radical metabolism, as detected by abnormal activities of critical antioxidant enzymes and other indices of lipid peroxidation in plasma, red blood cells, and cerebrospinal fluid. Such abnormalities have been associated with tardive dyskinesia, negative symptoms, neurological signs, poor premorbid function, and CT scan abnormalities. Studies to date have generally been exploratory. Further elucidation of the role of free radicals and antioxidants in schizophrenia and its treatment will require systematic investigation.

INTRODUCTION

There is abundant evidence that free radicals are involved in membrane pathology in the central nervous system (CNS),[1,2] and may play a role in neuropsychiatric disorders, including schizophrenia.[3] Although the nature and location of the membrane pathology in schizophrenia has yet to be elucidated, abnormalities in membrane structure and function have been reported, associated with alterations in membrane phospholipids, essential fatty acids, and signal transduction.[4,5] A separate body of evidence indicates impaired free radlcal pathology in schizophrenia, and will be reviewed here.

After a brief introduction to free radical metabolism, including the antioxidant defense system, and membrane pathology in schizophrenia, the review will examine the evidence in schizophrenia of free radical-mediated pathology. Further, the following important, and sometimes vexing, questions will be addressed: (i) do peripheral measures of abnormal free radical metabolism reflect similar pathological processes in the CNS?; (ii) are peripheral indices of membrane pathology of clinical utility?; (iii) are findings of abnormal indices of free radical metabolism specific to schizophrenia? If not, how does a common pathological event lead to varied clinical presentations? Finally, strategies to further systematically examine free radical-mediated pathology will be considered.

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Origin of free radicals

A consequence of aerobic metabolism is the generation of potentially toxic free radicals, which are chemical species with unpaired electrons. Free radicals (primarily the reactive oxygen species, superoxide and hydroxyl radicals) are generated in vivo during many normal biochemical reactions involving oxygen, including the mitochondrial electron transfer chain, NADPH-dependent oxidases, autoxidation of polyunsaturated fatty acids and catecholamines.[6–8] The superoxide radical is generated during reactions involving oxidases, auto-oxidation (in the presence of metal catalysts), and photolysis. Superoxide is catalytically converted by copper/zinc- and manganese-dependent superoxidase dismutases (SOD) to hydrogen peroxide. Although hydrogen peroxide is not a free radical, it is highly susceptible to autoxidation. In the presence of iron, which is present in significant concentrations in the central nervous system (CNS), hydrogen peroxide decomposes to yield the highly reactive hydroxyl radical.

Oxidative stress

Oxidative stress is a state where there is a dysequilibrium between pro-oxidant processes and the antioxidant defense system in favor of the former, and generally occurs as a consequence of increased production of free radicals, or when the antioxidant defense system is inefficient, or a combination of both events. Oxidative stress, regardless of the specific cause, can result in initiation of number of pathophysiological processes leading to cellular toxicity.

Free radicals target cellular components indiscriminately, including lipids, proteins, DNA, and carbohydrates. Protein oxidation can lead to loss of sulfhydryl groups, in addition to modifications of amino acids, leading to the formation of carbonyl moieties. Accumulation of oxidized proteins may result in losses of selected biochemical and physiological functions. Free radical-mediated damage can also affect cellular macromolecules, such as DNA, by destroying pathways critical to the maintenance of normal adenine and pyridine neuclotide status. These alterations can affect the viability of DNA and modify gene expression. Lipids, by virtue of their location in cell membranes, are particularly vulnerable to peroxidation, as discussed below.

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 antioxidant defense system, comprising a series of enzymatic and non-enzymatic 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 co-operatively at different sites in the metabolic pathway of free radicals (see Fig. 1).

Hydrogen peroxide produced by SOD is decomposed to water and oxygen by the heme protein, CAT, thereby preventing the formation of hydroxyl 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. Because 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.

The non-enzymatic antioxidant components consist of molecules that react with activated oxygen species and thereby prevent the propagation of free radical chain reactions (see Fig. 1). The most common non-enzymatic antioxidant molecules are glutathione, alpha-tocopherol (vitamin E). ascorbic acid (vitamin C), and beta-carotene.

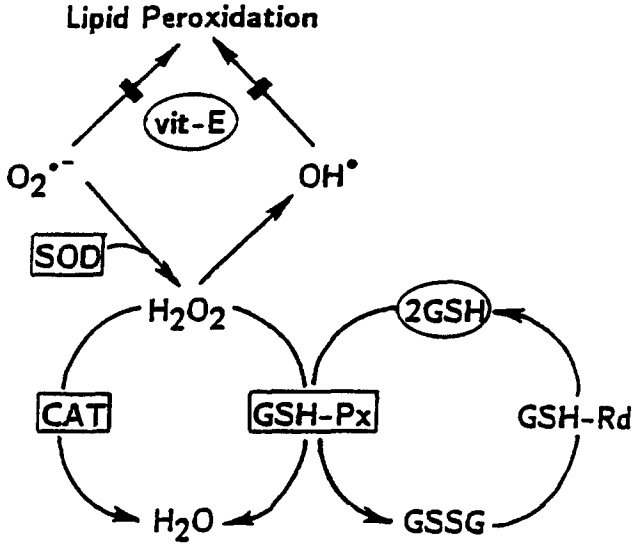

Fig. 1 Enzymatic antioxidant defense pathways. H_2O_2, hydrogen peroxide; H_2O water; $O_2^{\bullet-}$, superoxide radical; OH•, hydroxyl radical; GSH, reduced glutathione; GSSG, oxidized glutathione; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; GSH-Rd, glutathione reductase.

Free radicals and lipid peroxidation

Free radicals can cause peroxidative damage to lipids. Polyunsaturated fatty acids (PUFA), which are major components of membrane phospholipids, are highly susceptible to free radical insult and autoxidation to form peroxyradicals and lipid peroxide intermediates. The existence of peroxyradicals within cell membranes results in unstable membrane structure, altered membrane fluidity and permeability, and impaired signal transduction.[9] 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.[9] Aldehydes can react with lipids and proteins to form 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 PUFA and has virtually no cell turnover, is particularly vulnerable to free radical-mediated damage. The process of lipid peroxidation has many important physiological and pathological consequences.

There are potentially multiple pathological consequences of increased oxidative stress, owing either to increased free radical production and/or inefficient antioxidant systems (e.g. increased SOD and/or decreased CAT activity), that lead to lipid peroxidation. Such changes in free radical metabolism have implications for the pathophysiology of schizophrenia: (i) lipid peroxidation can alter polyunsaturated fatty acids (PUFA) content and such changes in PUFA have been reported in schizophrenic patients;[4,10] (ii) high levels of hydrogen peroxide and lipid peroxides lead to decreased synthesis of prostaglandins,[11] which also have been reported in schizophrenic patients;[4] (iii) lipid peroxidation is associated with increased dopamine and decreased GABA uptake by synaptosomes and may modulate brain GABA receptor function;[12–14] (iv) hydroxyl radicals decrease synaptic efficiency and impair action potential generation in hippocampal pyramidal cells,[15] (v) hydrogen peroxide can inhibit dopamine b-hydroxylase.[16] 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,[17] thus resulting in decreased catecholamine production.

Free radicals and membrane pathology

The accumulating evidence for membrane pathology in schizophrenia has recently been reviewed by Horrobin et al.[5] Membrane lipid pathology in schizophrenia was first reported by Stevens[18] in 1972, demonstrating in red blood cell (RBC) membranes a significant increase in phosphatidylserine, and decreases in phosphatidylcholine and phosphatidylethanolamine, findings that were later replicated by some studies and not by others.[19] Because PUFAs are the major constituents of membrane phospholipids, the discrepancies of RBC membrane phospholipid abnormalities observed in schizophrenic patients from different studies may be caused by a bimodal distribution of PUFAS in RBC membranes of schizophrenic patients.[20]

Fatty acid composition

The two series of the essential fatty acids (EFA) are omega-3 (n-3) and omega-6 (n-6), derived from dietary alpha-linolenic acid and linoleic acid respectively. Diverse and inconsistent EFA abnormalities have been found in the plasma and RBC membranes of schizophrenic patients, owing in part to differences in patient groups and methodolog.[21,22] In a clinical trial of EFA supplementation, Vaddadi et al[23] confirmed their previously reported low levels of EFA in schizophrenic patients. The above studies were mainly carried out in neuroleptic-treated schizophrenic patients. More recently, we[21] reported a significant decrease of PUFAs, particularly 18:2(n-6) and 20:4(n-6) series, in the RBC ghost membranes of schizophrenic patients on and off haloperidol treatment. Therefore, a decreased level of 18:2(n-6) in blood of schizophrenic patients appears to be a consistent finding.[21–25] Clinical trials of gamma-linolenic acid [18:3(n-6)] have shown modest therapeutic effects.[26–28]

Recently, Glen et al[20] reported an interesting relationship between fatty acid abnormalities and schizophrenic symptomatology. They found that patients with prominent negative symptoms (e.g. poverty of thought and anhedonia) were associated with high levels of saturated fatty acids and low levels of PUFAs in RBC membranes, in contrast to those with positive symptoms (hallucinations and delusions). Furthermore, in contrast to normal RBC membranes, schizophrenic patients exhibited a bimodal distribution in unsaturated fatty acids with 20 and 22 carbonatoms.

Membrane fluidity

The dynamic state, or fluidity, of the cell membrane is dependent on its composition and, in the intact cell, also influenced by motion imposed by the cytoskeleton. Small changes in membrane fluidity have been shown to have considerable effects on a wide variety of membrane functions. Specifically, alterations in membrane fluidity have been implicated in the regulation of the densities and binding affinities of neurotransmitters and neurohormones, including serotonin,[30] norepinephrine,[31] opiates[32] and dopamine.[33] Therefore, the reported changes in membrane phospholipid composition associated with schizophrenia may result in altered neurotransmission by virtue of a pertubation of membrane fluidity. Hitzemann et al[34] have previously demonstrated a significant increase in the steady-sate anisotropy (r_s) of DPH-labelled RBC ghost membranes from patients with schizophreniform disorder, but not with schizophrenia. In the same report, however, they also indicated that 5 of 8 schizophrenic patients had values higher than the highest control value. Later, Pettegrew et al[35] reported an increased molecular motion on the RBC membrane surface and in the phospholipid head group region in the unmedicated schizophrenic patients. No significant motional differences, however, were found in the membrane hydrocarbon core of the unmedicated patients. Recently, Yao et al[36] have reported a significant increase in rs values from schizophrenic patients withdrawn from haloperidol. Furthermore, changes in rs values of drug-free patients were significantly correlated with their increase in psychosis ratings. Therefore, decreased RBC membrane fluidity in schizophrenia is consistent with decreased PUFAs in RBC membranes.

^{31}P Nuclear magnetic resonance (^{31}P NMR)

Recently, with the introduction of ^{31}P NMR spectroscopy to study in vivo phosphorus metabolism of living subjects, Pettegrew et al[35] have demonstrated a significant reduction of phosphomonoesters (PME, phospholipid precursors) and significantly increased levels of phosphodiesters (PDE, phospholipid breakdown products) in neuroleptic-naive first-episode schizophrenic patients compared with the controls. In addition, an increased level of ATP and decreased inorganic orthophosphate levels were also found in the frontal cortex of schizophrenic patients. These authors suggest that changes in membrane phospholipids may be related to molecular changes that precede the onset of clinical symptoms and brain structural changes in schizophrenia, while changes in high energy phosphate metabolism may be state dependent. Similar findings in membrane phospholipid perturbations were also reported in both acutely and chronically ill patients by other groups.[37–40] These changes in membrane phospholipids might be caused by a degenerative process leading to cortical volume losses.[41–44] Furthermore, using ^{31}P NMR, Keshavan et al[45] have suggested a possible familial basis for membrane phospholipid changes in schizophrenia.

The observed alterations in membrane structure and function can be a consequence of free radical-induced pathology.[24] As discussed above, PUFAs are particularly vulnerable to free radical insult. Peroxidative damage of membranes can lead to losses of EFAs in phospholipids, decreased membrane fluidity, and subsequent receptor dysfunction.

FREE RADICAL-MEDIATED PATHOLOGY IN SCHIZOPHRENIA

Although a role for toxic radicals (adrenochromes) in the etiology of schizophrenia was proposed in the mid 1950s Hoffer et al[46] there has been limited investigation of free radical metabolism in schizophrenia. All studies to date have examined indirect measures of free radical activity, as direct measures of free radicals in vivo are difficult and cumbersome. The majority of studies have examined the activities of key antioxidant enzymes in plasma and erythrocytes, based on the premise that altered enzyme activities reflect oxidative stress. A few studies have examined levels of peroxidation products, which provide a more direct evidence of oxidative damage.

Studies of antioxidant enzymes

Of the critical antioxidant enzymes, SOD activity has been examined the most. Increased SOD activity has been reported in red blood cells (RBC) of schizophrenic patients by some,[47–53] but not by others.[54] Decreased SOD activity has been reported in neuroleptic-naive first-episode schizophreniform and schizophrenic patients, and found to be associated with impaired premorbid school functioning.[55] By contrast, GSH-Px activity was found to be lower, relative to normal controls, in neuroleptic-treated chronic schizophrenic patients,[56] in drug-free female schizophrenic patients[47] and in neuroleptic-naive psychotic children.[57] Decreased CAT activity has also been reported in schizophrenic patients.[51,58,59] Although the above studies show abnormalities in individual antioxidant enzymes, the physiology of the antioxidant defense system (Fig. 2) suggests that examining a single enzyme may have limited value for elucidating the role of abnormal free radical metabolism in disease processes.[60] Only one study to date has examined contemporaneously all three critical antioxidant enzymes in schizophrenic patients.[51] Relative to normal controls, chronic schizophrenic patients had elevated RBC SOD activity, decreased CAT activity, and no difference in GSH-Px activity. These findings are suggestive of oxidative stress. However, no indices of lipid peroxidation were available.

Studies of peroxidative damage

Evidence for peroxidative damage in schizophrenic patients, while limited, has also been consistent. Increased blood levels of malondialdehyde were found in schizophrenic patients relative to normal controls.[61–64] More critically, there is evidence of plasma lipid peroxidation at the onset of psychosis in never-medicated, first-episode schizophrenic patients.[65] Increased concentrations of pentane, a marker of lipid peroxidation, was found in schizophrenic patients relative to normal controls.[66,67] However, in the absence of measures of antioxidant enzymes in the above studies, the origin of the oxidative stress cannot be determined.

Postmortem studies

There has been only one report of a postmortem study of SOD activity in schizophrenia,[68] with no difference found between schizophrenic patients and control subjects, and only the diencephalon (thalamus, epi-, sub-, and hypothalamus) was examined. Because other brain areas, particularly the striatum and other cortical structures, were not examined, the significance of these findings remains unclear. By contrast, electron microscopic studies of brains from schizophrenics have found large amounts of lipofuscin-like material in oligodendrocytes,[69] abnormal pigment-laden neurons,[70] and axonal deposits of lipofuscin-like bodies.[71] As noted above, lipofuscin is a by-product of lipid peroxidation. While some studies have reported gliosis, a potential response to neuronal

loss, in schizophrenic patients, others have not.[72] However, cell death is not the only consequence of free radical-induced toxicity. It is Likely that increased levels of oxidative stress lead to membrane abnormalities and subsequent neuronal dysfunction.

Other observations

Unscheduled DNA synthesis (UDS) induced in lymphocytes by mutagens is one measure of DNA repair ability. Topinka et al[73] reported decreased UDS in schizophrenic patients, relative to normal controls, and also found increased lipid peroxidation products. Six weeks treatment with 600 mg/day of vitamin E resulted in increased UDS and decreased peroxidation indices.

Vitamin C levels have been measured in schizophrenic patients with disparate results, although in a carefully conducted study plasma and urinary vitamin C levels were found decreased, relative to normal controls, even after controlling for diet.[74] After vitamin C supplementation for 1 month, group differences were no longer significant. The authors suggested that vitamin C requirements for schizophrenic patients may be higher. Vitamin C is critical to the regeneration of vitamin E during its antioxidant function. Future studies should examine both vitamins C and E.

There have been no published studies of α-tocopherol or GSH levels in schizophrenic patients.

Clinical implications of free radical pathology

While the evidence of abnormal free radical metabolism in schizophrenia continues to accumulate, there is less certainty about its pathophysiological and clinical implications Buckman et al[75,76] found that platelet GSH-Px activity is inversely correlated with computed tomographic (CT) scan measures of brain atrophy in patients with chronic schizophrenia, specifically non-paranoid schizophrenia with a predominance of negative symptoms. We have reported a robust inverse relationship between RBC SOD activity and severity of neurological 'soft' signs in chronic schizophrenic patients.[77] Decreased SOD activity has been reported to be associated with impaired premorbid school functioning in neuroleptic-naive first-episode schizophreniform and schizophrenic patients.[55] Also in the neuroleptic-naive patients, plasma measures of lipid peroxidation (LP) were correlated with severity of negative symptoms, and with worsening of neurological 'soft' signs with neuroleptic treatment.[78,79] Prilipko[62] found, in schizophrenic patients, increased blood levels, relative to normal, with higher levels of LP products in patients with 'nuclear' schizophrenia compared to patients with 'process' schizophrenia. Albeit speculative, the above findings taken together suggest that free radical-mediated pathology is associated with features of schizophrenia associated with a poorer outcome.

Effect of neuroleptics on free radical metabolism

All biological investigations in schizophrenia have to contend with the potential confounding effects of neuroleptic treatment. This issue assumes greater importance in light of the available evidence from animal studies. Several studies[80–82] have reported variable changes of SOD, CAT, and GSH-Px activities in brain, and levels of lipid peroxidation with short-term neuroleptic treatment (7–60 days). In these studies SOD, CAT, and GSH-Px activities were generally elevated, and LP decreased, but no study found decreased CAT activity. However, data from animal studies allow only limited inference of neuroleptic effects because the treated animals have a baseline normal antioxidant defense system. The few studies in schizophrenic patients that have examined neuroleptic effects have reported variable findings. In one study that compared across groups, no significant difference was found in SOD and GSH-Px activities between schizophrenic patients on neuroleptics and those off neuroleptics for 3 months, or between manic-depressive patients on lithium alone and those on lithium and neuroleptics, and suggested that the altered antioxidant enzyme activities may be reflecting a disease-related process.[47] Buckman et al[76] did not find a relationship between peripheral GSH-Px activity and both short-term neuroleptic treatment and cumulative neuroleptic exposure. Similarly, Reddy et al[51] did not find a significant relationship between plasma haloperidol levels and RBC SOD, CAT, and GSH-Px. Lohr et al[83] also did not find, in schizophrenic patients, any relationship between cerebrospinal fluid (CSF) and conjugated dienes (lipid peroxidation products) and neuroleptic treatment, and more critically, did not find differences in levels of conjugated dienes between never-treated and neuroleptic-treated patients. However, increased CSF lipid peroxidation products have been reported in patients receiving phenothiazines, with greater levels in those experiencing Parkinsonian side effects,[84] and in other patients.[85] Initial data from a small sample of chronic schizophrenic patients, using a within-subject, repeated-measures, on-off neuroleptic study, showed that neuroleptic discontinuation was associated with decreasing SOD activity from a previously high level,[86] and with further lowering of CAT activity.[59] One possible explanation of these findings is that neuroleptics contribute to oxidative stress, leading to increased SOD activity and consequent increase in hydrogen peroxide production. This in turn induces CAT activity. With neuroleptic discontinuation, as in the above study, these processes are reversed. It is interesting that low RBC SOD has been found in never-treated first-episode patients,

relative to normal controls.[55] Follow-up studies in this patient population could provide more robust evidence of neuroleptic effects. Furthermore, there may be differential effects of conventional neuroleptics and atypical neuroleptics such as clozapine and risperidone. We are beginning to examine these issues in never-medicated first-episode psychotic patients.

An interesting, but potentially important, observation is the risk for clozapine-induced agranulocytosis in patients with decreased RBC levels of GSH-Px and selenium.[87]

Free radicals and tardive dyskinesia

About 20% of patients receiving neuroleptics long term develop tardive dyskinesia. Therefore, the general consensus is that neuroleptics are necessary, but not sufficient, for the development of tardive dyskinesia (TD),[88] although some have argued that TD is integral to the schizophrenic disease processes.[89] Free radical-mediated pathology has been implicated in the development of TD.[90,91] Lohr et al[81] found significantly higher levels of lipid peroxidation products (diene conjugates) in the cerebrospinal fluid of schizophrenic patients with TD than those without TD. They also demonstrated that the severity of TD was positively correlated with levels of diene conjugates, and more critically, high levels of diene conjugates were associated with subsequent development of TD. Evidence of oxidative stress in the CSF of patients with tardive dyskinesia has similarly been reported.[93] Recently, Peet et al[94] found a highly significant correlation between plasma levels of lipid peroxidation products and dyskinesia severity. Zubenko and Cohen[95] have shown that platelet membrane fluidity is altered in patients with TD, but not in similarly neuroleptic-treated patients without TD.

Vitamin E and schizophrenia

Indirect, but persuasive evidence for a role of free radicals in TD comes from treatment studies with vitamin E (alpha-tocopherol). Vitamin E is a highly efficient lipid-soluble 'chain-breaking' antioxidant that acts to stabilize plasma membranes. Numerous studies in animals and humans have demonstrated protective effects of vitamin E against a large variety of free radical-mediated pathological insults.[96,97] The use of supra-normal doses of vitamin E in psychiatry has been limited to its use in the treatment of TD and psychosis in schizophrenia. Recent studies utilizing double-blind design have reported decreases in the severity of dyskinesia by vitamin E treatment,[94,98–104] but not by others.[105,106] A shorter duration of TD was associated with better therapeutic response. Most studies utilized a dose range of 1200–1600 IU/day. However, Peet et al[94] found clinically significant responses with 1200 IU/day, with the therapeutic effect maintained for 7–13 months after discontinuation of vitamin E. In one study, significant decreases in psychiatric symptoms (rated on the Brief Psychiatric Rating Scale, BPRS) were found in schizophrenic patients following vitamin E treatment.[107] If, indeed, free radicals play a role in the development of TD, patients with an inadequate antioxidant defense system would be more likely to develop TD.

THE UTILITY OF EXAMINING PERIPHERAL INDICES OF FREE RADICAL METABOLISM

A critical issue is whether peripheral indices (RBC and plasma) of abnormal free radical metabolism, as examined in most studies, reflect similar changes in the CNS and/or are related to presumed CNS events. As noted previously, platelet GSH-Px activity is inversely related to cortical sulcal prominence on CT scan.[75,76] In Down's syndrome, the increased CNS SOD is correlated with REC SOD activity.[108] The increased RBC GSH-Px activity is also correlated with IQ in patients with Down's syndrome.[109] In addition, RBC activities of SOD and CAT are differentially altered in those patients with and without manifestations of Alzheimer's disease.[110] Several other studies have also shown peripheral and central alterations in AODS enzymes in dementia syndromes,[111,115] and increased basal levels of lipid peroxidation in the frontal cortex of Alzheimer's patients.[116] To study the relationship between CNS and RBC SOD activity, Abdalla et al[117] found that both enzymes were increased 72 h after injection of 6-hydroxydopamine into lateral ventricles of chlorpromazine-treated and untreated Wistar rats. These authors suggest that activation of CNS-SOD is caused by an increased superoxide production resulting from autoxidation of 6-hydroxydopamine to semiquinones. Semiquinones can cross the blood–brain barrier to the bone marrow and, through a process similar to that occurring in CNS, induce SOD in RBC. Furthermore, chronic stress in rats results in an increased SOD activity in both brain and blood, increased lipofuscin accumulation and decreased phospholipids in the CNS, with alterations in behavior and vegetative functions correlating with biochemical changes.[118] Therefore, it appears reasonable to use blood components in examining the issue of free radical-mediated pathology in schizophrenia. Furthermore, it is possible that peripheral indices of free radical metabolism (e.g. levels of lipid peroxides) can have clinical utility, such as identification of patients at higher risk for developing tardive dyskinesia or developing clozapine-induced agranulocytosis.[87]

Whether abnormalities found in both neural and extraneural tissues have the same functional consequences also needs consideration. There are several paradigmatic conditions such as Down's syndrome, phenylketonuria,

and various lipidoses, where the enzymatic abnormalities are expressed in both neural and peripheral tissues, but the functional consequences are most profound in the CNS. The CNS is uniquely vulnerable to free radical-mediated damage because of its high PUFA content, high metabolic rate, and high content of metal catalysts. While elevated SOD/decreased CAT activity in RBC may not produce significant peripheral pathology, similar alterations of these enzymes in specific brain areas could lead to membrane dysfunction, and subsequent motor and cognitive disturbances. The evidence of increased cerebrospinal fluid lipid peroxidation products in patients with TD[83] suggests such a possibility. Furthermore, neuropathological changes[92] consistent with free radical-mediated pathology have been found in patients with TD.

It must be recognized that any peripheral pathological finding will ultimately need to be identified in the CNS. New and developing technologies, such as positron emission tomography, magnetic resonance imaging (MRI) and spectroscopy, and functional MRI are beginning to provide first glimpses into the living brain. No similar and easily accessible techniques are currently available to study free radical metabolism. Postmortem brain tissues provide an alternative solution, but have significant limitations – tissue is generally available from the elderly where there are age-related changes in oxidative stress; the effects of apoptosis; concomitant serious medical illnesses, including CNS pathology unrelated to schizophrenia; absence of antemortem assessments; and, uncontrolled nature of the sample. In spite of these limitations, the use of post-mortem brain tissue can be useful in providing confirmatory evidence of free radical pathology in schizophrenia.

THE SPECIFICITY OF FINDINGS TO SCHIZOPHRENIA

Free radical-mediated pathology has been implicated in several other neuropsychiatric disorders.[119] The schizophrenia-like psychosis and motor dysfunction of locura manganica ('manganese madness') associated with manganese toxicity, is believed to be mediated by enhanced autoxidation of catecholamines by manganese, resulting in altered binding of dopaminergic and cholinergic receptors, and neuronal degeneration in the substantia nigra.[120] A role for free radical-mediated pathology also has been proposed for Parkinson's disease,[121,123] supported by evidence of abnormalities in free radical metabolism in the substantia nigra,[123–128] and in dementia syndromes. Degeneration of striatal dopaminergic tracts in the MPTP model of Parkinson's disease is probably mediated by free radicals.[129]

It then must be asked – if free radical-induced pathology is not specific to schizophrenia, how may similar molecular mechanisms account for apparently dissimilar clinical syndromes? It has been suggested that the neuroanatomical location of a defect(s) in protective mechanisms may explain the variable expression of disease processes,[130] and subtle site-specific lesions caused by free radicals may eventually be of major consequence in the development of several pathological conditions.[131] Furthermore, the consequences of lipid peroxidation depend upon membrane PUFA content, pattern of protective enzymes, the nature of extracellular matrix,[132] and a variety of extracellular factors, such as age, nutritional status, hormonal influences, and stress.[133] There may be both genetic and developmental (epigenetic) factors that determine specific vulnerability to oxyradical-mediated neuronal dysfunction. Both regional variability and significant interindividual differences in antioxidant enzymes activity is known.[134] While SOD and GSH-Px are present in all areas of the brain, CAT is distributed primarily in the hippocampus, nucleus A6 of locus coeruleus, zona compacta of the substantia nigra, and ependymal cells lining the 3rd and 4th ventricles.[135] Pathological changes in some of these brain areas have been implicated in schizophrenia.[72,136]

FUTURE DIRECTIONS

The enthusiasm in investigating free radical-mediated pathology in neuropsychiatric disorders, and schizophrenia in particular, stems from the implications of this avenue of research. First, the hypothesis of free radical-induced membrane pathology has sufficient explanatory power with regard to many clinical and biological observations in schizophrenia, and ultimately is testable. Second, free radical-mediated pathogenetic mechanisms are accessible to pharmacological and dietary interventions. The former has already been utilized in the treatment of tardive dyskinesia with vitamin E. Future studies will have to systematically examine the role of diet in modifying oxidative stress. More immediately, consideration should be paid to using antioxidants adjunctively in the treatment of schizophrenia.

With regard to specific directions for research, the above review provides some guidance. Absent from the body of evidence is the systematic examination of critical indices of free radical metabolism in well-characterized schizophrenic patients. Studies in neuroleptic-naive first-episode psychotic patients using a within-subject repeated-measures design will be critical in answering questions regarding neuroleptic effects. Furthermore, studies of baseline measures of antioxidant status, with longitudinal follow-up, can examine their predictive value in determining a variety of outcome measures, such as side effects, relapse, deficit syndrome, and recovery. We and other laboratories are beginning to examine these issues.

Whether abnormalities of free radical metabolism are causally related to 'schizophrenia' per se is an important question, and can be addressed in part only with significant resources, involving high-risk studies in offspring of parents with chronic psychoses. One approach that can yield useful information is the use of twin studies or sib-pairs discordant for schizophrenia. A combination of research paradigms, including high-risk studies, studies in first-episode patients, and double-blind antioxidant treatment studies, likely will yield the most useful information on the specific role that free radicals have in the pathogenesis of schizophrenia and its subsequent course.[137]

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