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Implications for reactive oxygen species in schizophrenia pathogenesis

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ABSTRACT

Oxidative stress is a well-recognized participant in the pathophysiology of multiple brain disorders, particularly neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. While not a dementia, a wide body of evidence has also been accumulating for aberrant reactive oxygen species and inflammation in schizophrenia. Here we highlight roles for oxidative stress as a common mechanism by which varied genetic and epidemiologic risk factors impact upon neurodevelopmental processes that underlie the schizophrenia syndrome. While there is longstanding evidence that schizophrenia may not have a single causative lesion, a common pathway involving oxidative stress opens the possibility for intervention at susceptible phases.

1. Introduction

Studies into the etiology and pathogenesis of schizophrenia have implicated a vertiginous array of abnormalities of varied neurotransmitters, cell types, brain regions and epidemiologic associations. One can search the medical literature for most bodily chemicals and find suggestions of tie-ins to schizophrenia. Major lines of research seek to integrate the roles of genetic liability, neurodevelopmental anomalies, aberrant synapse function, and environmental factors such as neonatal infections and substance use, yet the manner in which these distinct factors coalesce into the neurobiology of schizophrenia is largely unknown (Brown, 2011; Keshavan et al., 2011; Tsuang, 2000; van Os et al., 2008). In this review we explore how oxidative stress (and its interrelationship with inflammation) may unify many of these disparate appearing mechanisms. A wide body of evidence finds increased oxidative stress in schizophrenia, including in subjects never previously treated with antipsychotic medication (Emiliani et al., 2014; Yao and Keshavan, 2011). We suggest that many genetic and environmental risk factors for schizophrenia are associated with oxidative stress and inflammation, and outline how these may adversely impact neurodevelopmental and neuromodulatory processes relevant to the neurobiology of schizophrenia.

Eukaryotes generate the bulk of their energy via mitochondria, whose bioenergetic roles include the Krebs cycle, ATP synthesis/oxidative phosphorylation, and oxidation of fatty acids and amino acids. As with most physiologic processes, such metabolism is not 100% efficient and comes with some caveats, particularly the generation of toxic byproducts such as superoxide (O_2^-) and hydroxyl radicals that are prone to damage DNA, enzymes, proteins, lipid, and carbohydrate, among other cellular components. These reactive oxygen species (ROS), broadly referred to as “oxidative stress”, are held in check by families of protective enzymes whose reduction–oxidation (“redox”) reactions convert harmful free radicals into benign, less-reactive molecules. Among these enzymatic families are catalase, the superoxide dismutases, thioredoxins, and over twenty enzymes that utilize glutathione as a cofactor (glutathione peroxidases and glutathione S-transferases). Dysregulation or overwhelming of these protective systems contributes to an increasing number of human diseases in which oxidative stress and inflammation occur, including neurodegenerative disorders such as dementia and amyotrophic lateral sclerosis, and more subtle alterations involved in aging (Haigis and Yankner, 2010; Radak et al., 2011; von Bernhardi and Eugenin, 2012).

Inflammatory processes are exquisitely tied to oxidative stress. The immune system generates lethal quantities of reactive oxygen and nitrogen species to do away with infectious diseases, eliciting inflammation in part via cytokines released by immune cells and microglia. NADPH

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oxidase, for instance, generates superoxide to dispatch with microbes, but at the cost of bystander damage to native tissue (Quinn et al., 2006).

Early development and adolescence are highly dynamic phases of brain development that may be prone to dysfunction that increases the risk of developing schizophrenia (Coyle and Enna, 1976; Crews et al., 2007; Goldman-Rakic and Selemon, 1997; Huttenlocher, 1979; Huttenlocher and de Courten, 1987; Jensen, 2002; Paus et al., 2008; Rakic et al., 1994; Sahara et al., 2012; Tarazi et al., 1998; Thompson and Nelson, 2001; Weinberger, 1987). Myelination, pruning of glutamate synapses, and maturation of interneurons are dynamic processes of this period (Fig. 1). The goal of this review is to highlight how many distinct schizophrenia risk factors converge upon oxidative stress pathways that may perturb neurobiology relevant to schizophrenia.

2. Many schizophrenia risk factors converge upon oxidative stress and inflammation

Environmental influences have long been implicated as schizophrenia risk factors, as identical twins have a 50% concordance rate for schizophrenia and first degree relatives have a 5–10% risk. Important environmental risks include prenatal and birth complications such as hypoxia, neonatal infections, season of birth, drug abuse and autoimmune disease (Brown, 2011). How is it that such vastly different risk factors can increase the risk of schizophrenia? One potential explanation is that these heterogeneous risk factors all are associated with increased in oxidative stress and inflammation. This perturbation of oxidative stress, especially during sensitive stages of brain development, may adversely impact the brain circuitry relevant to development

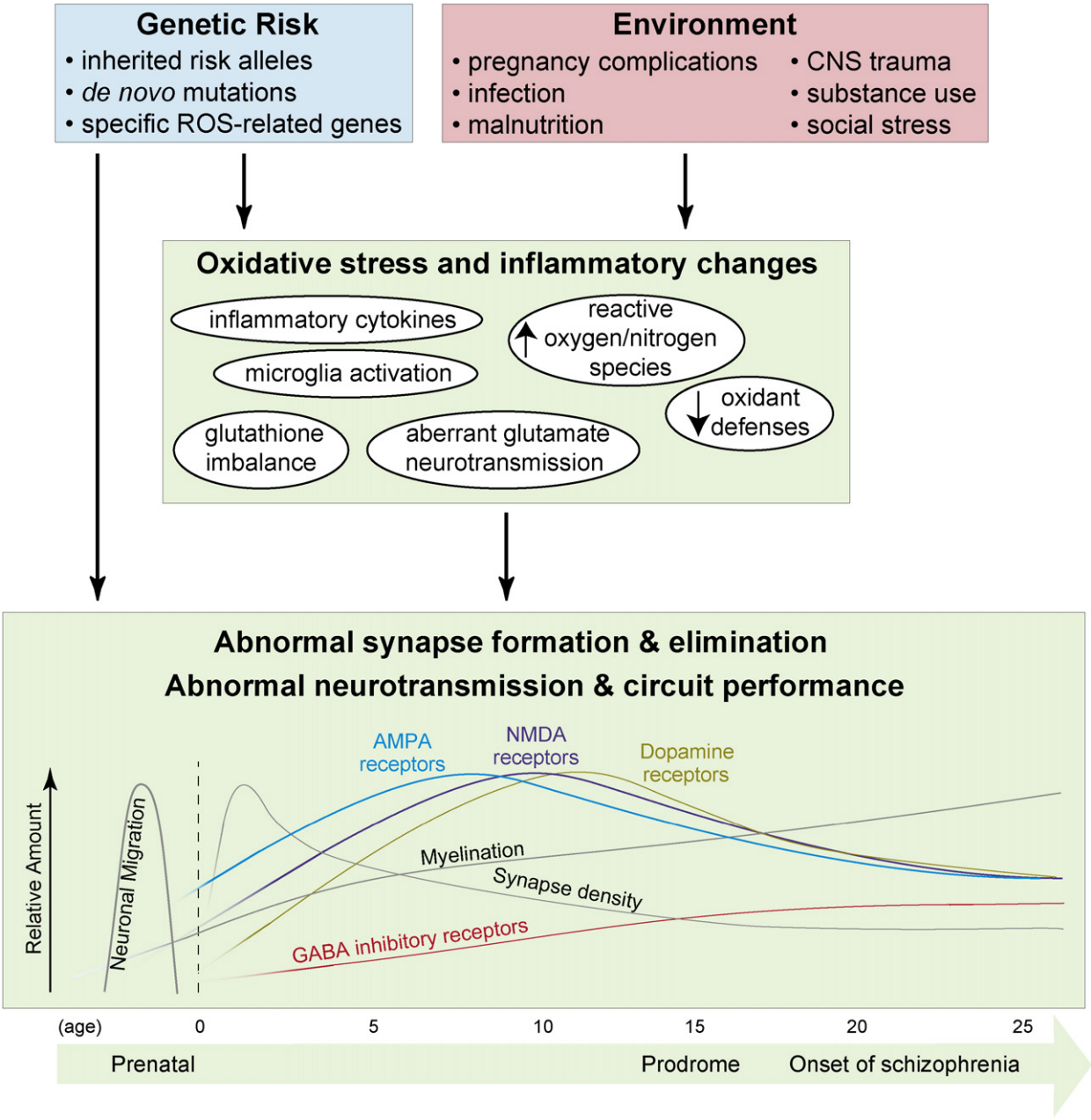

Fig. 1. Redox homeostasis bridges schizophrenia risk factors to brain abnormalities in schizophrenia. Impaired redox homeostasis may be impacted upon by genetic, epigenetic and environmental factors. Such redox abnormalities may impact upon brain abnormalities relevant to schizophrenia, including neurodevelopment, synapse formation, and neurotransmission. The 5:1 ratio of glutamate:GABA neurons is not shown to scale.
Graph compiled from Coyle and Enna (1976), Insel et al. (1990), Tarazi and Baldessarini (2000), Thompson and Nelson (2001), Ewald and Cline (2009), and Huttenlocher (1979).