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Review

Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A "central hub" in schizophrenia pathophysiology?

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ABSTRACT

Accumulating evidence points to altered GABAergic parvalbumin-expressing interneurons and impaired myelin/axonal integrity in schizophrenia. Both findings could be due to abnormal neurodevelopmental trajectories, affecting local neuronal networks and long-range synchrony and leading to cognitive deficits. In this review, we present data from animal models demonstrating that redox dysregulation, neuroinflammation and/or NMDAR hypofunction (as observed in patients) impairs the normal development of both parvalbumin interneurons and oligodendrocytes. These observations suggest that a dysregulation of the redox, neuroimmune, and glutamatergic systems due to genetic and early-life environmental risk factors could contribute to the anomalies of parvalbumin interneurons and white matter in schizophrenia, ultimately impacting cognition, social competence, and affective behavior via abnormal function of micro- and macrocircuits. Moreover, we propose that the redox, neuroimmune, and glutamatergic systems form a "central hub" where an imbalance within any of these "hub" systems leads to similar anomalies of parvalbumin interneurons and oligodendrocytes due to the tight and reciprocal interactions that exist among these systems. A combination of vulnerabilities for a dysregulation within more than one of these systems may be particularly deleterious. For these reasons, molecules, such as N-acetylcysteine, that possess antioxidant and anti-inflammatory properties and can also regulate glutamatergic transmission are promising tools for prevention in ultra-high risk patients or for early intervention therapy during the first stages of the disease.

1. Introduction

Schizophrenia is considered a disorder with an important neurodevelopmental component. Various genetic and environmental risk factors can affect brain developmental processes including maturation of interneurons and oligodendrocytes, which could eventually contribute to the emergence of the symptoms during adolescence and early adulthood (Insel, 2010). Our current understanding of the neurobiological processes involved in schizophrenia remains, however, limited. Many hypotheses have been proposed, but a consensus among the research community is lacking. Prominent hypotheses include disturbance of glutamatergic neurotransmission in the form of hypofunction of NMDA receptors (NMDARs) (Krystal et al., 1994; Coyle et al., 2012; Kantrowitz and Javitt, 2012; Steiner et al., 2013), neuroinflammation (Saetre et al., 2007; Potvin et al., 2008; van Berckel et al., 2008; Meyer, 2013), and redox dysregulation (Do et al., 2009a,b; Clay et al., 2011; Gysin et al., 2011; Martins-de-Souza et al., 2011; Yao and Keshavan, 2011). We propose that dysregulation of redox homeostasis, neuroimmune, and glutamatergic systems induced by different etiological factors constitute, via their reciprocal interactions, one "central hub" as a common final pathway contributing to this disorder (Fig. 1). Here, we review the effect of dysregulation of each of these systems and their interactions on excitatory/inhibitory balance of local neuronal circuits (microcircuits), as well as the connections between distant brain areas (macrocircuits). In particular, we propose that dysfunction in these systems has deleterious effects on normal development of cortical and hippocampal parvalbumin-expressing interneurons (PVIs), which are essential for fast local neuronal synchronization, and on oligodendrocytes, which form myelin sheets around axons providing fast signal conduction between the brain regions. Anomalies of PVIs and oligodendrocytes are indeed widely recognized in schizophrenia and considered to contribute to abnormal brain connectivity leading to cognitive, affective, and social deficits.

2. A "hub" formed by the redox, glutamatergic, and neuroimmune systems

A dysregulation of the redox, glutamatergic, and neuroimmune systems has all been reported in schizophrenia. Genetic and/or

Abbreviations: NAC, N-acetylcysteine; PN, pyramidal neuron; PNN, perineuronal net; PVIs, parvalbumin interneurons; RNS, reactive nitrogen species; ROS, reactive oxygen species.

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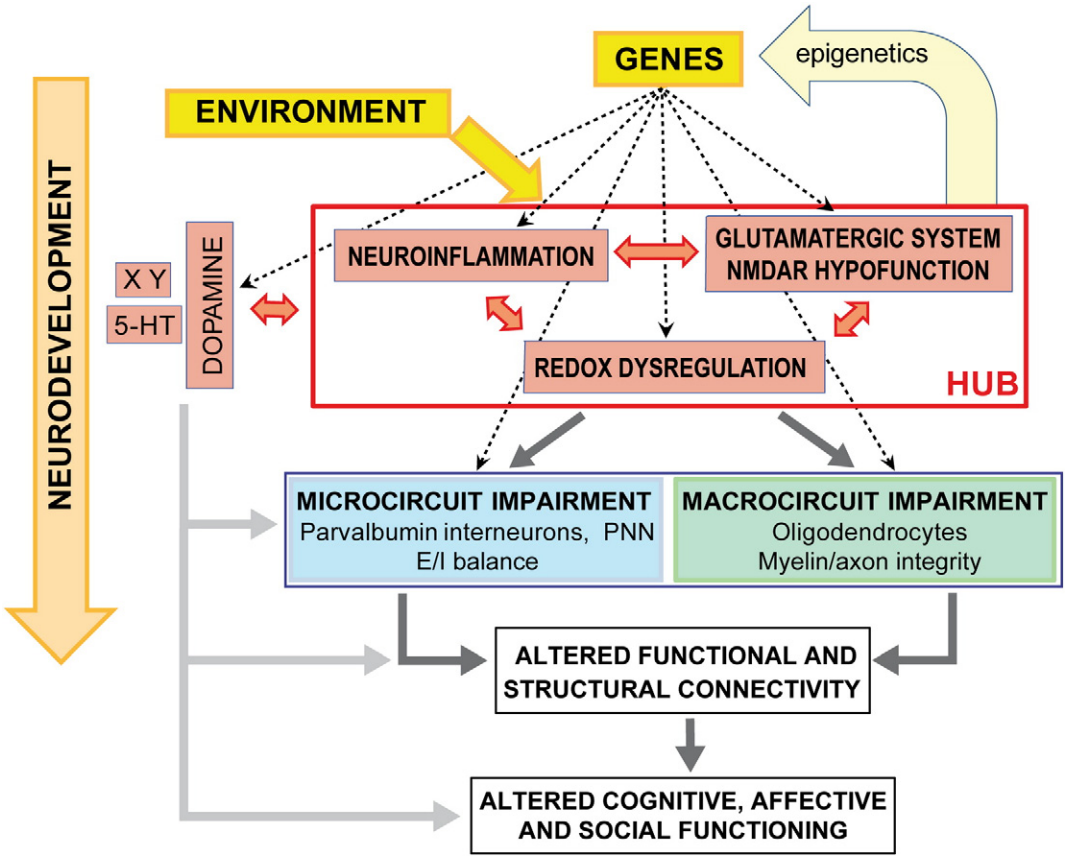

Fig. 1. Proposed "hub" formed of the redox, neuroimmune, and glutamatergic systems whose dysregulation during development could disrupt maturation of parvalbumin interneurons (PVIs) and oligodendrocytes, two cell types affected in schizophrenia and critical for short- and long-range neuronal network synchronization. This could impact structural and functional connectivity circuits affecting diverse aspects of cognitive, affective and social functioning (Buckholtz and Meyer-Lindenberg, 2012). Genetic risk factors combined with environmental insults can affect the homeostasis of one or several of the "hub" systems which in turn could impact the others through reciprocal interactions (*reciprocal arrows*). Genetic vulnerability to redox dysregulation in schizophrenia is supported by polymorphisms and copy number variations in genes related to the GSH metabolism (Tosic et al., 2006; Gysin et al., 2007; Rodriguez-Santiago et al., 2010; Gravina et al., 2011; Mehta et al., 2013). In addition, impaired function of proteins coded by other plausible risk genes, including *DISC1*, *PROD*, *G72*, *NRG*, *DTNBP1*, indirectly leads to oxidative stress often via mitochondrial dysfunction (Goldshmit et al., 2001; Krishnan et al., 2008; Park et al., 2010; Clay et al., 2011; Gokhale et al., 2012; Johnson et al., 2013). Genes related to the immune system have also been identified as potent risk genes for schizophrenia, in particular the major histocompatibility complex (*MHC*) genes, one of the most replicated genetic risk factors for schizophrenia disorder (Stefansson et al., 2009; Smyth and Lawrie, 2013). Finally, genetic vulnerability for NMDAR hypofunction seems to be more associated with potent risk genes encoding proteins that indirectly influence the function of this receptor; this includes D-amino acid oxidase, G72, dysbindin, and neuregulin (see Coyle et al., 2012), mGluR5 and proteins belonging to the postsynaptic NMDAR complex (Kirov et al., 2012; Timms et al., 2013; Fromer et al., 2014; Purcell et al., 2014). Developmental insults that are known to increase the risk for schizophrenia cause redox dysregulation/oxidative stress (Walter et al., 2002; Do et al., 2009b) and/or neuroinflammation (Schiavone et al., 2009; Brenhouse and Andersen, 2011; Garate et al., 2013; Kaur et al., 2013). Note that the dopaminergic or serotoninergic (5-HT) systems (and others = X Y) modulated by risk-factor genes and environment could also impact micro- and macrocircuits either directly or indirectly via interactions with the above "hub". *Dotted arrows* depict impact of genetic risk factors. E/I balance: excitatory/inhibitory balance; PNN: perineuronal net surrounding PVIs.

environmental risk factors can contribute to disturbances within each of these tightly interdependent systems (see Fig. 1 and its legend for more details). In particular, redox pathways represent a central node via their numerous reciprocal interactions with the glutamatergic and immune systems. Oxidative stress is defined as an imbalance between antioxidants and pro-oxidants (reactive oxygen species (ROS) and reactive nitrogen species (RNS)), resulting in macromolecular damage. In addition, redox signaling plays a key regulating role in many cellular and physiological processes (Jones, 2008). A redox dysregulation can affect cell proliferation/differentiation, energy metabolism, and neurotransmission via an alteration of redox-sensitive protein function, redox-dependent gene expression, and epigenetic mechanisms (Valko et al., 2007; Cyr and Domann, 2011; Ray et al., 2012). Several proteins related to glutamatergic neurotransmission contain modulatory redox sites, including glutamine synthase (Mustafa et al., 2007), serine racemase (responsible for synthesis of glycine, a NMDAR co-agonist (Pinteaux et al., 1996)), and NMDARs (Choi et al., 2001). While redox state modulates NMDAR function, activation of synaptic NMDARs strengthens neuronal antioxidant defense mechanisms (Hardingham and Bading, 2010). Moreover, glutathione (GSH), the main antioxidant and redox regulator, constitutes a neuronal reservoir of glutamate (Koga et al., 2011). These observations indicate that redox and glutamatergic systems are intimately dependent. Likewise, oxidative stress is tightly linked to inflammation. Many inflammatory mediators are activated by oxidative molecules, while activated immune cells such as microglia generate ROS and RNS. The complex interplay between oxidative stress and inflammation is in part governed by the reciprocal interactions between the transcription factors Nrf2 (whose nuclear translocation induces antioxidant phase II gene transcription) and NF-κB (whose translocation to the nucleus promotes transcription of many pro-inflammatory genes) (Buelna-Chontal and Zazueta, 2013). Finally, an imbalance of the immune system may also affect NMDAR function. Human subjects with anti-NMDAR encephalitis develop psychosis (Dalmau et al., 2011) and antibodies against NMDAR have been reported in patients diagnosed with schizophrenia (Steiner et al., 2013). Moreover, inflammatory processes cause increased production of kynurenic acid, an endogenous NMDAR antagonist, via dysregulation of tryptophan/kynurenine metabolism (Muller et al., 2011). Thus, redox, immune, and glutamatergic systems form a triad in which each of its elements can influence the others. Diverse genetic vulnerabilities and environmental risk factors may affect one element of this triad, impacting in turn the other systems. Because of the complex interactions between