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Schizophrenia is primed for an increased expression of depression through activation of immuno-inflammatory, oxidative and nitrosative stress, and tryptophan catabolite pathways

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ABSTRACT

Schizophrenia and depression are two common and debilitating psychiatric conditions. Up to 61% of schizophrenic patients have comorbid clinical depression, often undiagnosed. Both share significant overlaps in underlying biological processes, which are relevant to the course and treatment of both conditions. Shared processes include changes in cell-mediated immune and inflammatory pathways, e.g. increased levels of pro-inflammatory cytokines and a Th1 response; activation of oxidative and nitrosative stress (O&NS) pathways, e.g. increased lipid peroxidation, damage to proteins and DNA; decreased antioxidant levels, e.g. lowered coenzyme Q10, vitamin E, glutathione and melatonin levels; autoimmune responses; and activation of the tryptophan catabolite (TRYCAT) pathway through induction of indoleamine-2,3-dioxygenase. Both show cognitive and neurostructural evidence of a neuroprogressive process. Here we review the interlinked nature of these biological processes, suggesting that schizophrenia is immunologically primed for an increased expression of depression. Such a conceptualization explains, and incorporates, many of the current perspectives on the nature of schizophrenia and depression, and has implications for the nature of classification and treatment of both disorders. An early developmental etiology to schizophrenia, driven by maternal infection, with subsequent impact on offspring immuno-inflammatory responses, creates alterations in the immune pathways, which although priming for depression, also differentiates the two disorders.

1. Introduction

The etiology, biological course and treatment for schizophrenia and clinical depression still remain largely elusive. Current conceptualizations of both disorders are viewed as distinct. Models of schizophrenia have centered on an early developmental etiology, strongly driven by maternal infections during pregnancy, with subsequent alterations in N-methyl D-aspartate receptor (NMDAr) activity (Adell et al., 2012), driving alterations in dopaminergic, gamma-aminobutyric acid (GABA)-ergic and glutamatergic neuronal activity. Depression, on the other hand, is classically thought to be driven by decreased serotonin (Maes and Meltzer, 1995).

The prevalence of depression in schizophrenia is high, with rates up to 61% of previously undiagnosed depression in schizophrenic patients in one study (Gozdzik-Zelazny et al., 2011), suggesting an overlap in biological processes in schizophrenia and depression. Comorbidity of depression and schizophrenia is the essence of schizoaffective disorder, a term used to denote a subtype of schizophrenia (DSM-IIIR, 1987). In people with psychosis at first presentation a diagnosis of schizoaffective

Abbreviations: NMDAr, N-methyl D-aspartate receptor; GABA, gamma-aminobutyric acid; O&NS, oxidative and nitrosative stress; TRYCAT, tryptophan catabolite; SNP, single nucleotide polymorphism; NOS, nitric oxide synthase; COX-2, cyclooxygenase-2; sPLA2, secretory phospholipase A2; ROS, reactive oxygen species; GSH, glutathione; XO, xanthine oxidase; MDA, malondialdehyde; PUFA, polyunsaturated fatty acid; IgM, immunoglobulin M; SOD, superoxide dismutase; CSF, cerebral spinal fluid; CMI, cell mediated immune; IO&NS, immuno-inflammatory and O&NS; IL, interleukin; IFN, interferon; IL-2R, IL-2 receptor; TGF, transforming growth factor; TH, T helper; TNF, tumor necrosis factor; sIL-2R, soluble IL-2 receptor; IL-1RA, IL-1 receptor antagonist; CIRS, compensatory anti-inflammatory response syndrome; PGE2, prostaglandin E2; MMP-3, matrix metalloproteinase-3; NAS, N-acetylserotonin; IDO, indoleamine 2,3-dioxygenase; TDO, tryptophan 2,3-dioxygenase; cAMP, cyclic adenosine 3′,5′-mono-phosphate; KYNA, kynurenic acid; KAT, kynurenine aminotransferase; QUIN, quinolinic acid; 7αAChr, alpha 7 nicotinic acetylcholine receptor; 3-OHK, 3-hydroxykynurenine; CUMS, chronic unpredictable mild stress; FGFr1, fibroblast growth factor receptor-1; CNS, central nervous system; NAC, N-acetyl-cysteine; BAG-1, Bcl-2 associated athanogene-1; PPI, prepulse inhibition; GSK-3, glycogen synthase kinase-3β.

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disorder is very low, at 0.2%. However, within two years the level of schizoaffective disorder increases to more than 12% (Salvatore et al., 2009). The data by Gozdzik-Zelazny et al. (2011) suggests that the level of comorbid depression with schizophrenia increased further over time, and is underdiagnosed. A diagnosis of schizoaffective disorder has historically been one of the most controversial concepts in psychiatric nosology (Robert, 1987). Such confusion and controversy are still evident today (Heckers, 2012), driven by the very low diagnostic reliability for schizoaffective disorder (Maj et al., 2000). Statistically, without reliability there can be no validity.

It remains unclear if depressive symptoms are a core feature of schizophrenia, represent true comorbidity, or are unrelated epiphenomena. One position views depressive symptoms as a core feature of schizophrenia (Birchwood et al., 2000; Johnson, 1981), founded on the severity and prevalence of depression in schizophrenia (an der Heiden et al., 2005). Factor analytic studies of the symptoms of schizophrenia suggest that depressive symptoms are equivalent to positive and negative psychotic symptoms in the disorder (Arora et al., 1997; Ventura et al., 2000). Opposing views are that depressive symptoms in schizophrenia are a potential side-effect of neuroleptics, movement disorder, reflection of negative symptoms, substance use disorders, or an understandable reaction to the consequences of the disorder (Birchwood et al., 1993; Harrow et al., 1994; Prosser et al., 1987; Siris, 1987; Turkington et al., 2009). These have largely been discounted (Siris, 2000).

Recent conceptualizations of both disorders have centered on the dysregulation of the immune system, cytokines, oxidative and nitrosative stress (O&NS) as well as the tryptophan catabolite (TRYCAT) pathway (Maes et al., 1990; Smith and Maes, 1995). This places the emergence of depression in schizophrenia in the same ballpark as the increased depression rates in the neurodegenerative/neuroinflammatory disorders, including Alzheimer's disorder, multiple sclerosis, Parkinson disorder and stroke, all of which are associated with immuno-inflammatory and O&NS changes in the course of the disorders, and have very high levels of comorbid depression (Maes et al., 2011b).

Here, we review the neurobiological nature of the comorbidity of depression with schizophrenia, suggesting that the biological underpinnings are commonalities in immuno-inflammatory, O&NS and TRYCAT pathways.

2. Oxidative and nitrosative stress (O&NS) pathways

The brain, because of its high metabolic rate, is more vulnerable to the effects of O&NS. Even mild psychosocial stressors, e.g. examination stress, induce inflammatory and Thelper (TH)-1-like responses and increase oxidative damage to DNA and lipids, as well as decreasing plasma antioxidants (Maes et al., 1999; Sivonova et al., 2004; Wadee et al., 2001).

2.1. O&NS and depression

Depression is comorbid with many psychiatric, neurodegenerative and general medical conditions (Maes et al., 2011b). A common denominator of these disorders, and their overlaps with depression, include changes in O&NS pathways. Single nucleotide polymorphisms (SNPs) and increased mRNA expression in O&NS associated genes, including manganese superoxide (SOD), inducible (iNOS) and neuronal (nNOS) nitric oxide synthase (NOS), myeloperoxidase, cyclooxygenase-2 (COX-2) and secretory phospholipase A2 (sPLA2)-IIA are associated with depression (Galecki et al., 2010a, 2011, 2012). Alterations in O&NS pathways, concurrent with heightened inflammatory pathways, are key components of depression (Leonard and Maes, 2012; Maes, 2008). Increased O&NS in recurrent episodes contributes to neuroprogression in depression (Berk, 2009; Maes et al., 2011a, 2012; Moylan et al., in press). Neuroprogression is a stage related and potentially deteriorating process involving the combination of impaired neuroplasticity, reduced neurogenesis coupled to increased apoptosis and neurodegeneration (Berk, 2009; Maes et al., 2012b,c). The 2–3% decrement in cognitive ability after each depressive episode in people with recurrent depression (Gorwood et al., 2008) and associated increased risk of subsequent Alzheimer's disease exemplifies the nature of neuroprogression (Kessing and Andersen, 2004).

The induction of reactive oxygen species (ROS) is necessary for most normal cellular functions, driving signaling, plasticity and adaptation. However, the ability to adapt to and switch off endogenously produced oxidants and to induce endogenous antioxidants is crucial to the maintenance of homeostasis. Depression is accompanied by significantly lower plasma concentrations of important antioxidants, such as vitamin E, zinc, glutathione (GSH), coenzyme Q10, selenium, and a lowered total antioxidant status (Jacka et al., in press; Kodydkova et al., 2009; Maes et al., 2000, 2009a; Pasco et al., 2012; Szewczyk et al., 2011). Decreased plasma alpha-tocopherol correlates with increased severity of depression (Owen et al., 2005). Decreased antioxidants enhance O&NS damage to lipids, proteins and DNA (Maes et al., 2009b). Increased ROS, as indicated by plasma peroxides and xanthine oxidase (XO) is evident in depression (Herken et al., 2007). Further indicants of O&NS damage include increased malondialdehyde (MDA), a by-product of polyunsaturated fatty acid (PUFA) peroxidation (Khanzode et al., 2003), which correlates with impaired declarative and working memory (Talarowska et al., 2012a); and increased 8-hydroxy-2-deoxyguanosine, which is a marker of oxidative damage to DNA (Forlenza and Miller, 2006; Maes et al., 2009b). Significantly elevated levels of oxidative and lipid peroxidation products in depressed patients compared to controls have been found, which reversed with treatment (Maes et al., 2011a). Not all studies show such changes in oxidant status after treatment (Galecki et al., 2009).

Melatonin, a powerful endogenous antioxidant, induces mitochondrial oxidative phosphorylation, has anti-inflammatory effects and entrains circadian rhythms (Maldonado et al., 2009; Martín et al., 2002). Decreased synthesis of melatonin in depression is associated with a SNP in acetylserotonin methyltransferase, the enzyme at the last step in melatonin synthesis (Galecki et al., 2010b). This is coupled with a melatonin receptor SNP susceptibility gene for recurrent depression (Galecka et al., 2011). Decreased melatonin levels and receptor effects will contribute to the dysregulation of O&NS in depression, as well as to changes in circadian, immune and inflammatory regulation in both depression and schizophrenia (Anderson and Maes, 2012a).

NO is synthesized from L-arginine by constitutive and iNOS. NO, like ROS, has many functions in normal processes, including vasodilatation, neurotransmission and immunomodulation. When NO interacts with superoxide, the resultant peroxynitrite anions and peroxynitrous acid can damage lipid membranes. The L-arginine-NO pathway is involved in depression and the working mechanism of antidepressants (Pinto et al., 2008). Measurements of NO in depressed patients have produced mixed results (Ozcan et al., 2004). Increased iNOS along with COX-2, myeloperoxidase and sPLA2-IIa has been found in patients with recurrent depression (Galecki et al., 2012). Maes et al. (2011d) found increased levels of immunoglobulin M (IgM) directed against multiple NO-adducts in depression, indicating chronically increased NO and/or peroxynitrite levels (Maes, 2008; Maes et al., 2011d). Increased plasma NO correlates with decreased declarative and working memory (Talarowska et al., 2012b), and is associated with increased suicide attempts (Kim et al., 2006). The administration of omega-3 PUFAs to rodents decreases the levels of NO and other oxidants in the hypothalamus and may be relevant to the efficacy of omega-3 PUFAs in depressive disorders (Songur et al., 2004). Generally increased NO in association with O&NS will have deleterious consequences relevant to changes seen in depression.

2.2. O&NS and schizophrenia

Evidence shows that O&NS pathways are involved in the pathophysiology of schizophrenia via lipid peroxidation, DNA damage and