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INFLAMMATORY CYTOKINES IN DEPRESSION: NEUROBIOLOGICAL MECHANISMS AND THERAPEUTIC IMPLICATIONS☆

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Abstract—Mounting evidence indicates that inflammatory cytokines contribute to the development of depression in both medically ill and medically healthy individuals. Cytokines are important for development and normal brain function, and have the ability to influence neurocircuitry and neurotransmitter systems to produce behavioral alterations. Acutely, inflammatory cytokine administration or activation of the innate immune system produces adaptive behavioral responses that promote conservation of energy to combat infection or recovery from injury. However, chronic exposure to elevated inflammatory cytokines and persistent alterations in neurotransmitter systems can lead to neuropsychiatric disorders and depression. Mechanisms of cytokine behavioral effects involve activation of inflammatory signaling pathways in the brain that results in changes in monoamine, glutamate, and neuropeptide systems, and decreases in growth factors, such as brain-derived neurotrophic factor. Furthermore, inflammatory cytokines may serve as mediators of both environmental (e.g. childhood trauma, obesity, stress, and poor sleep) and genetic (functional gene polymorphisms) factors that contribute to depression's development. This review explores the idea that specific gene polymorphisms and neurotransmitter systems can confer protection from or vulnerability to specific symptom dimensions of cytokine-related depression. Additionally, potential therapeutic strategies that target inflammatory cytokine signaling or the consequences of cytokines on neurotransmitter systems in the brain to prevent or reverse cytokine effects on behavior are discussed. **© 2013 IBRO. Published by Elsevier Ltd. All rights reserved.**

Key words: inflammatory cytokines, depression, serotonin, dopamine, brain-derived neurotrophic factor, kynurenines.

Contents

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Abbreviations: 5-HIAA, 5 hydroxyindoleacetic acid; 5-HT, serotonin; 5-HTT, 5-HT transporter; ACTH, adrenocorticotropic hormone; AIAQ, anger irritability and assault questionnaire; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BCG, bacille Calmette–Guerin; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; BH2, dihydrobiopterin; BH4, tetrahydrobiopterin; CCL2, chemokine (C–C motif) ligand 2; CES-D, Center for Epidemiological Studies-Depression Scale; CFQ, Chalder fatigue questionnaire; CIDI, Composite International Diagnostic Interview; CIRS-G, Cumulative Illness Rating Scale Geriatric; COMT, catechol-*O*-methyltransferase; COX2, cyclooxygenase 2; CRH, corticotropin releasing hormone; CRHR1, CRH receptor 1; CRP, C-reactive protein; CSF, cerebrospinal fluid; DA, dopamine; DAMPs, danger-associated molecular patterns; DAT, dopamine transporter; DHA, docosahexaenoic acid; DISC1, disrupted in schizophrenia 1; DR, DA receptor; DYNLT1, dynein light chain Tctex-type 1; FDOPA, [18F]fluorodopa; FKBP5, FK506 binding protein 5; GCH1, GTP cyclohydrolase 1; GR, glucocorticoid receptor; HADS, Hospital Anxiety and Depression Scale; HCV, hepatitis C virus; HDRS, Hamilton Depression Rating Scale; HIV, human immunodeficiency virus; HPA, hypothalamic–pituitary–adrenal; IDO, indoleamine-2,3-dioxygenase; IFN, interferon; IFN-AR, IFN-alpha receptor; IL, interleukin; iNOS, inducible NO synthase; IRAK, IL-1 receptor-associated kinase; KA, kynurenic acid; KYN, kynurenine; LPS, lipopolysaccharide; M.I.N.I, Mini International Psychiatric Interview for DSM-IV Axis I Disorders; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemotactic protein-1; MHPG, 3-methoxy-4-hydroxyphenylglycol; NE, norepinephrine; NF, nuclear factor; NMDA, *N*-methyl-D-aspartate; NMDAR, NMDA receptor; NO, nitric oxide; NOSs, NO synthases; P2X7, purinergic type 2X7; PAH, Phen hydroxylase; PEG, pegylated; PET, positron emission tomography; PGE2, prostaglandin E2; Phen, phenylalanine; PLA2, phospholipase A2; POMC, proopiomelanocortin; PSQI, Pittsburgh Sleep Quality Index; QUIN, quinolinic acid; ROS/RNS, reactive oxygen and nitrogen species; SAMe, *S*-adenosyl-methionine; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders; SDS, Zung self-rating depression scale; SNPs, single-nucleotide polymorphisms; SSRIs, selective serotonin reuptake inhibitors; TNF, tumor necrosis factor; TOR1B, torsin family 1, member B; Tyr, tyrosine; VMAT2, vesicular monoamine transporter 2.

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INTRODUCTION

There has been a great deal of interest in the effects of cytokines of the innate immune system on the brain and behavior. Cytokines are important in brain development, and can promote healthy brain function by supporting neuronal integrity, neurogenesis, and synaptic remodeling (Yirmiya and Goshen, 2011). Cytokines also have the capability of influencing neurocircuitry and neurotransmitter systems to produce behavioral alterations (Miller et al., 2009; Haroon et al., 2012). Acutely, administration of cytokines or activation of the innate immune system can induce a behavioral repertoire termed ''sickness behavior'' that includes anhedonia, anorexia, fever, sleep changes, and decreased social interaction (Dunn and Swiergiel, 1998; Dunn et al., 2005; Dantzer and Kelley, 2007). These potentially adaptive behavioral responses to cytokines can benefit an organism by promoting conservation of energy and allocation of resources to combat infection or recovery from injury, along with behaviors that may elicit care-giving from others (Lotrich, 2012). However, under conditions of chronic exposure to elevated inflammatory cytokines, persistent alterations in neurotransmitter function and behavior can lead to the development neuropsychiatric dysfunction, and especially depression. For instance, patients with increased inflammatory cytokines due to a variety of medical illnesses have increased rates of depression compared to the general population (Yirmiya et al., 1999, 2000), and some patients with idiopathic major depression without co-morbid medical illness also exhibit increased circulating cytokines and inflammatory markers (Maes et al., 1992; Maes, 1999; Sluzewska, 1999; Dowlati et al., 2010). Furthermore, administration of cytokines to humans and laboratory animals produces neuropsychiatric symptoms and behavioral alterations consistent with depression (Miller et al., 2009).

To address the role of cytokines in depression, this review will provide an overview of the current literature from both human and animal studies regarding the effects of inflammatory cytokines on brain neurocircuitry and neurotransmitter systems that lead to behavioral change (mechanisms of cytokine actions in the brain summarized in Fig. 1). We should note that not all types of depression necessarily involve cytokines, e.g. post-partum and peri-menopausal depression, hypothyroidism, depression secondary to cocaine withdrawal, and vascular depression to name just a few. Therefore, depression that is associated with inflammatory cytokines may be one subtype of depression. Nonetheless, it is biologically plausible that inflammatory cytokines serve as mediators of both environmental and genetic factors that may trigger the development of depressive disorders (Raison and Miller, 2011). Factors that may precipitate inflammation and influence the development of depression include medical illness, obesity, psychosocial stress, sleep disturbance, and gastrointestinal inflammation, and will be discussed herein. Additionally, there is growing interest in the iatrogenic depression that results from exogenous interferon-alpha therapy. This has facilitated mechanistic research interest into prospectively determining the pathways by which depression develops during inflammatory cytokine exposure. This set of various endogenous inflammatory cytokine and exogenous cytokine-associated depressions has been associated with specific risk factors that may allow for potential preventive interventions. That is, not all subjects exhibiting increased inflammatory cytokines develop depression, and there are numerous vulnerability and resilience factors for cytokine-induced depression (Kendler et al., 2001; Caspi et al., 2003; Duman and Monteggia, 2006; Heim et al., 2008; Lotrich, 2011) Moreover, the role of the immune system in depression suggests potential novel and targeted therapeutic strategies for reversing cytokine effects on the brain and behavior, which will be reviewed.

CYTOKINES AND DEPRESSION

Elevated cytokines and inflammatory markers in idiopathic major depression

Numerous studies have reported increases in circulating proinflammatory cytokines, interleukin (IL)-1, IL-6, tumor

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