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Review article

Cytokines and major depression

Olga J.G. Schiepers, Marieke C. Wichers*, Michael Maes

Department of Psychiatry and Neuropsychology, Maastricht University, P.O. BOX 616, 6200 MD Maastricht, The Netherlands

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Abstract

In the research field of psychoneuroimmunology, accumulating evidence has indicated the existence of reciprocal communication pathways between nervous, endocrine and immune systems. In this respect, there has been increasing interest in the putative involvement of the immune system in psychiatric disorders. In the present review, the role of proinflammatory cytokines, such as interleukin (IL)-1, tumour necrosis factor (TNF)-α and interferon (IFN)-γ, in the aetiology and pathophysiology of major depression, is discussed. The 'cytokine hypothesis of depression' implies that proinflammatory cytokines, acting as neuromodulators, represent the key factor in the (central) mediation of the behavioural, neuroendocrine and neurochemical features of depressive disorders. This view is supported by various findings. Several medical illnesses, which are characterised by chronic inflammatory responses, e.g. rheumatoid arthritis, have been reported to be accompanied by depression. In addition, administration of proinflammatory cytokines, e.g. in cancer or hepatitis C therapies, has been found to induce depressive symptomatology. Administration of proinflammatory cytokines in animals induces 'sickness behaviour', which is a pattern of behavioural alterations that is very similar to the behavioural symptoms of depression in humans. The central action of cytokines may also account for the hypothalamic–pituitary–adrenal (HPA) axis hyperactivity that is frequently observed in depressive disorders, as proinflammatory cytokines may cause HPA axis hyperactivity by disturbing the negative feedback inhibition of circulating corticosteroids (CSs) on the HPA axis. Concerning the deficiency in serotonergic (5-HT) neurotransmission that is concomitant with major depression, cytokines may reduce 5-HT levels by lowering the availability of its precursor tryptophan (TRP) through activation of the TRP-metabolising enzyme indoleamine-2,3-dioxygenase (IDO). Although the central effects of proinflammatory cytokines appear to be able to account for most of the symptoms occurring in depression, it remains to be established whether cytokines play a causal role in depressive illness or represent epiphenomena without major significance.
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Keywords: Cytokines; Depression; HPA axis; IDO; Immune activation; Psychoneuroimmunology; Serotonin

Contents

Abbreviations: ACh, acetylcholine; ACTH, adrenocorticotropic hormone; ANS, autonomous nervous system; APP, acute-phase protein; BBB, blood–brain barrier; CAA, competing amino acid; CMS, chronic mild stress; CNS, central nervous system; CRH, corticotropin-releasing hormone; CS, corticosteroid; DA, dopamine; HPA, hypothalamic–pituitary–adrenal; 5-HT, 5-hydroxytryptamine (serotonin); IBD, inflammatory bowel disease; ICSS, intracranial self-stimulation; i.c.v., intracerebroventricular; IDO, indoleamine-2,3-dioxygenase; IFN, interferon; IL, interleukin; IL-1ra, interleukin-1 receptor antagonist; i.p., intraperitoneal; IRS, inflammatory response system; LNAA, large neutral amino acid; LPS, lipopolysaccharide; MAO, monoamine oxidase; MS, multiple sclerosis; NA, noradrenaline; NK, natural killer; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide; NTS, nucleus tractus solitarius; OB, olfactory bulbectomised; 3OH-KYN, 3-hydroxy-kynurenine; OVLT, organum vasculosum laminae terminalis; PG, prostaglandin; QUIN, quinolinic acid; RA, rheumatoid arthritis; ROS, reactive oxygen species; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant; TNF, tumour necrosis factor; TRP, tryptophan; VP, vasopressin.

* Corresponding author. Tel.: +31 43 3299785; fax: +31 43 3299708.
E-mail address: m.wichers@sp.unimaas.nl (M.C. Wichers).

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1. Introduction

From a psychoneuroimmunological perspective, the brain is no longer regarded as an immunopriviliged organ that is separated entirely from circulating immune cells by the blood–brain barrier (BBB) and displays reduced or altered immune responsivity. In the last decades, it has become clear that many interactions occur between neural, immune and neuroendocrine systems (Fig. 1; Plaut, 1987; Felten and Felten, 1991; Cserr and Knopf, 1992; Ader et al., 1995; McGeer and McGeer, 1995).

The concept of bidirectional communication between the immune system and the central nervous system (CNS) has led to the question whether the immune system, besides playing a role in normally occurring brain–immune interactions, is also involved in neuropathological processes (Miller et al., 1999). One of the psychiatric disorders that is assumed to be related to changes in the functional activity of the immune system, is major depression. Dysregulation of the functional activity of the immune system in depression is a phenomenon that has been demonstrated numerous times (Kronfol et al., 1983; Irwin and Gillin, 1987; Maes, 1995, 1999; Nunes et al., 2002). In 1999, Maes proposed the 'IRS model of major depression', which implies that major depression is related to activation of the inflammatory response system (IRS). According to this model, major depression may be considered a psychoneuroimmunological disorder, in which peripheral immune activation, through the release of proinflammatory cytokines, is responsible for the variety of behavioural, neuroendocrine and neurochemical alterations that are associated with this psychiatric condition. Besides the 'IRS model of major depression', this assumption has also been expressed as the 'macrophage theory of depression' (Smith, 1991; Leonard and Song, 1999; Leo-

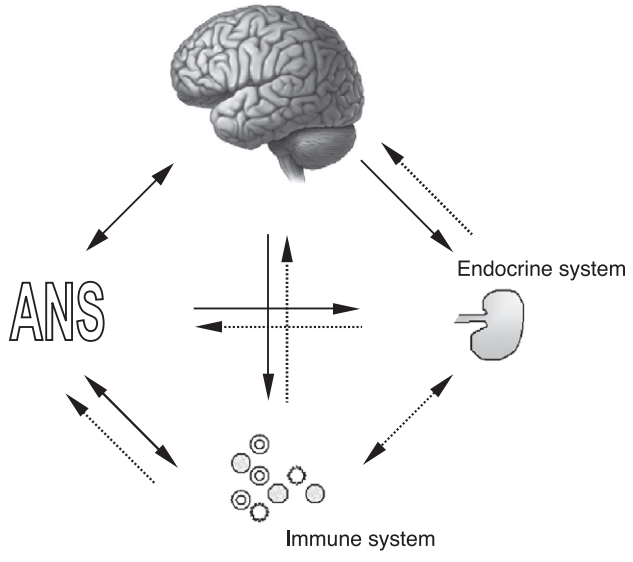

Fig. 1. Communication pathways between the central systems of the brain and other body systems. Most routes are bidirectional. Solid lines indicate neural connections, dashed lines indicate humoral connections and open arrows indicate interactions with body or environment. (Adapted and modified from Shepherd, 1994b).

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