



The significance of proinflammatory cytokines and Th1/Th2 balance in depression and action of antidepressants

Teruhisa Komori^{†,1}

ABSTRACT

In the last 25 years, many reports have indicated that the enhancement of cell-mediated immunity is well recognized in depression, including increased levels of proinflammatory cytokines, which induce sickness behavior. In particular, there has been much interest in the metabolic pathway, from tryptophan to kynurenine. Excessive amounts of proinflammatory cytokines may activate this pathway in depression, resulting in the reduced production of serotonin and increased neurodegenerative products. Neurodegeneration might be involved in the atrophy of several brain regions. However, the reported action of antidepressants on immune function has not been consistent: they have been reported to cause both the suppression and enhancement of proinflammatory cytokines. Furthermore, the effects of antidepressants on the T helper (Th)1/Th2 balance are poorly understood. It is speculated that alterations in the Th1/Th2 balance might result from homeostatic maladjustment in depression, while antidepressants may act as an immunomodulator. What is currently known about proinflammatory cytokines in depression, and the immunomodulatory effects of antidepressant treatments are reviewed.

Keywords

Depression, Immunomodulation, Proinflammatory cytokines, Th1/Th2 balance

Introduction

Research in the last 25 years has indicated that the acceleration of cell-mediated immunity is well recognized in depression. The main findings are increased proinflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor (TNF)- α . Olfactory bulbectomized (OB) rodents are a useful model of depression because they present with changes in both humoral and cellular immunity. Similar changes are found in patients with major depression [1]. Furthermore, studies of the immune system of OB rats indicated that different types of antidepressants counteracted immune changes induced by the lesions [1]. We previously reported that the ratio of Lyt 2-positive suppressor T cells to L3T4-positive T helper cells in OB mice was decreased,

suggesting that bulbectomy activates immune function [2]. We also reported that chronic, but not acute, imipramine administration significantly increased this ratio in both sham-operated (SO) and OB mice, resulting in a normalized ratio in OB mice [2]. These findings in OB animals suggest that immune function is activated in depression and that antidepressants suppress immune function. In clinical studies, proinflammatory cytokines are attracting increasing attention. It has been suggested that inflammatory cytokines are increased in depression and are suppressed by antidepressants [1], but actual findings are inconsistent with this theory. This review describes what is currently known about proinflammatory cytokines in depression, the action of antidepressants and the

¹Professor, Department of Stress and Health Science, Mie University Graduate School of Medicine, 2-174, Edobashi, Tsu, Mie 514-8507, Japan

[†]Author for correspondence: Professor Teruhisa Komori, MD, Department of Stress and Health Science, Mie University Graduate School of Medicine, 2-174, Edobashi, Tsu, Mie 514-8507, Japan; Tel: +81(059)231-5095, email: komori@nurse.medic.mie-u.ac.jp

effects of antidepressants on the T helper (Th)1/Th2 balance.

■ Proinflammatory cytokines in depression

Depression has been characterized as a disorder with a multifactorial etiology. Recently, the role of immunomodulation, in particular proinflammatory cytokines, was reported [1]. Dowlati *et al.* [3] conducted a meta-analysis of nine cytokines in major depression by assessing 24 studies. They concluded that basal levels of interleukin (IL)-6 and TNF- α were significantly elevated. A study comparing 1132 depressed patients and 494 healthy subjects showed a significant increase in C-reactive protein (CRP) and serum IL-6 in depressed males, but not females [4]. Such clinical observations suggest that a close relationship exists between proinflammatory cytokines and major depression. This is the basis of the hypothesis that the inflammatory response is important in depression. Although some proinflammatory cytokines are produced in the brain, most proinflammatory cytokines are produced in peripheral immune tissues and during disease traffic through the leaky blood-brain barrier, which affects various brain functions [5].

Proinflammatory cytokines induce sickness behavior similar to symptoms of depression [6]. Recently, there has been much interest in the metabolic pathways from tryptophan to kynurenine [7]. Tryptophan has two metabolic pathways that synthesize either serotonin or kynurenine and kynurenic acid. In the kynurenic acid pathway, a key enzyme indoleamine 2,3-dioxygenase is activated by proinflammatory cytokines. Excess levels of proinflammatory cytokines may activate indoleamine 2,3-dioxygenase in depression, thereby reducing serotonin production [8]. Following the formation of kynurenine, there are two further metabolic pathways of tryptophan [7]. Kynurenine is first metabolized to 3-hydroxykynurenine by kynurenine hydroxylase, and then to quinolinic acid. In glia and neurons, 3-hydroxykynurenine quinolinic acid enhances apoptosis [8]. Conversely, kynurenine can be metabolized by kynurenine aminotransferase to produce kynurenic acid, which has neuroprotective effects [8]. In patients with depression, neurodegeneration is often dominant and might be involved in the atrophy of several brain regions [8]. Compared with healthy subjects, depressed patients have a reduced gray

matter volume in several brain regions, especially the limbic system [9]. Although some patients undergo remission from the initial depression episode, repeat disease episodes often occur. This might be related to organic changes in the brain [1]. It has been hypothesized that systemic low-grade inflammation may result in various diseases such as depression and cardiovascular disease; in which proinflammatory cytokines play a key role [10].

Proinflammatory cytokines stimulate the hypothalamus-pituitary-adrenal axis to induce increased levels of glucocorticoid and decrease the sensitivity of glucocorticoid receptors, resulting in glucocorticoid resistance. Therefore, cellular immunity is enhanced and a vicious circle is initiated in which proinflammatory cytokines are further increased [8].

■ Immunomodulatory effects of antidepressants

It has been assumed that both pharmacological and non-pharmacological anti-depressive treatments have significant effects on activated immune-inflammatory pathways. Furthermore, antidepressant treatments may have anti-inflammatory properties, thereby suppressing macrophage functions [11]. In an animal study, antidepressants significantly suppressed hypersensitivity reactions. Desipramine suppressed hypersensitivity by 55% and fluoxetine by 42% compared with the positive control [12]. However, the effect of antidepressants on immune function has not been consistently reported.

According to the meta-analysis of 22 studies consisting of 603 depressed patients [13], depressive symptoms improved but changes in the levels of inflammatory cytokine were varied. Treatment with antidepressants decreased IL-1 β and probably IL-6, while TNF- α was not decreased. In terms of antidepressants, selective serotonin reuptake inhibitors (SSRI) decreased IL-6 and TNF- α , but other antidepressants did not appear to decrease inflammatory cytokines. Recently, paroxetine was reported to inhibit lipopolysaccharide (LPS)-induced IL-6 production but enhanced LPS-induced TNF- α production in mouse macrophages [14]. A large cohort study [4] showed that CRP and serum IL-6 increased as an inflammatory response in males who remitted using serotonin and norepinephrine reuptake inhibitors and CRP increased in males and females who remitted with tricyclic or tetracyclic antidepressants (TCAs). However, IL-6 was decreased in males

who remitted using selective SSRI. Imipramine attenuated IL-6 responses in mouse plasma [15]. Findings regarding the effect of TCAs on IL-6 have been inconsistent [16]. TCAs enhance neurotransmission in noradrenergic and serotonergic systems to different extents. Therefore, it is difficult to evaluate the effect of TCAs on cytokine production [16].

It was reported that antidepressant drugs increased the cellular concentration of cyclic adenosine monophosphate and suppressed the secretion of proinflammatory cytokines through the serotonin receptor [17] or other intracellular pathway [18]. Therefore, the action of serotonin on the immune function is related to serotonin transport to immune cells [18].

Despite conflicting experimental findings, fluoxetine appears to modulate immune responses. Thus, when the basal immune function is high, fluoxetine administration reduces lymphocyte activity. However, low basal immune function can be recovered by fluoxetine treatment [18]. Normalization of immune function is not always linked to the use of antidepressants or immune modulating-medication, as cytokine plasma levels normalize during recovery from acute depressive episodes in major depressive disorder patients who are unmedicated. This might be a very significant result to help understand the relationship between immune function and depression. The finding that the normalization of cytokines may be related to the recovery of depression *per se*, and not because of an anti-inflammatory effect of antidepressants, is of importance for the development of improved depression treatments [19].

■ Th1/Th2 balance

A review by Martino *et al.* [16] highlighted the influence of antidepressants on immune function. It has been reported that glucocorticoids, norepinephrine (NE), and epinephrine suppress Th1-related cytokines, such as IL-1 β , IL-2, interferon (IFN)- γ and TNF- α via the stimulation of glucocorticoid receptors, and upregulate Th2-related cytokines, such as IL-4, IL-10, and IL-13, through stimulation of β 2 adrenergic receptors, resulting in a Th1 shift [20]. In contrast, the effects of serotonin are complicated. Physiological doses of serotonin induce the secretion of proinflammatory cytokines such as IL-1 β , IFN- γ , and TNF- α , while at excessive doses the secretion of these proinflammatory cytokines

were decreased in depressed patients [21]. The effect of neurotransmitters on the Th1/Th2 balance is complicated in depression because of the variety of factors involved, including the neurotransmitter dose and receptor subtype expression [22]. Long-term treatment with SSRI increased Th1-related cytokines and decreased Th2-related cytokines in depressed patients [23]. Thus, serotonin may mediate a Th1 shift. In a whole blood assay *in vitro*, both citalopram and escitalopram increased IL-1 β in depressed patients [24]. However, a clinical study indicated that escitalopram increased the level of IL-1 receptor antagonist and contributed toward a Th2 shift [25]. Venlafaxine, a serotonin and norepinephrine reuptake inhibitor, was also reported to have complex actions on cytokine levels. Venlafaxine decreased IL-6 in human hippocampal cells [26]. In a clinical study, low doses of venlafaxine reduced IL-6, whereas in an animal study higher doses increased IL-6 [27]. Some studies reported that bupropion, a norepinephrine-dopamine reuptake inhibitor, reduced TNF- α , IFN- γ , and IL-1 β , but increased IL-10 in LPS-stimulated human monocytes [28]. Therefore, bupropion may alter the Th1/Th2 balance towards a Th2 shift. Other antidepressants might affect more complex neurotransmission pathways, further complicating the effect of drugs on the Th1/Th2 balance [16].

■ Changes in the Th1/Th2 balance

Generally, acute mild stress causes Th2 activation. In contrast, chronic or repeated stress leads to Th1 activation. Th1 activation induced by chronic stress may depend on interactions between genetic, epigenetic, infective, tumoral, and environmental factors. Acute stress overlapping chronic stress can induce new temporary Th2 shifts [10]. Antidepressants affect serotonin and NE neurotransmission. The degree of effect on the two systems, neuroimmunomodulation induced by a balance between serotonin and NE are different according to the type of antidepressants administered. Neuroimmunomodulation induced by changes in the serotonin and NE balance might influence the Th1/Th2 cytokine balance. Therefore, it could be hypothesized that antidepressants that more strongly increase NE compared with serotonin increase Th2 cytokine production, while antidepressants that strongly increase serotonin decrease Th2 cytokine production. Antidepressants might not have any meaningful effects on the Th1/Th2 balance, but rather they appear to compensate for an

imbalance in Th1/Th2 numbers. The balance of Th1/Th2 might reflect the neurobiological background of different patients [16].

Although there have been many reports indicating that depression and the action of antidepressants are accompanied by oscillations in Th1/Th2 levels, the implications of this remain unclear. Oscillations in Th1/Th2 levels might be because of maladjustment in depression, or that antidepressants act as immunomodulators.

Conclusion

The pathology of depression and the action of antidepressants related to inflammatory cytokines and the Th1/Th2 balance are unclear. However, immunological changes reflect changes in brain functions and even whole body conditions. It is also unclear whether antidepressants act directly or indirectly on the immune system, but immunological changes may be important to understanding the action of antidepressants.

References

- Leonard BE. The concept of depression as a dysfunction of the immune system. *Curr. Immunol. Rev* 6(3), 205-212 (2010).
- Komori T, Yamamoto M, Matsumoto T, et al. Effects of imipramine on T cell subsets in olfactory bulbectomized mice. *Neuropsychobiol* 46(4), 194-196 (2002).
- Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol. Psychiat* 67(5), 446-457 (2009).
- Vogelzangs N, Duivis HE, Beekman ATF, et al. Association of depressive disorders, depression characteristics and antidepressant medication with inflammation. *Transl. Psychiatry* 2(2), e79 (2012).
- Gadek-Michanlska A, Tadeusz J, Rachwalska P, et al. Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems. *Pharmacol. Rep* 65(6), 1655-1662 (2013).
- Shattuck EC, Muehlenbein MP. Towards an integrative picture of human sickness behavior. *Brain. Behav. Immun* 57(1), 255-262 (2016).
- Won E, Kim YK. Stress, the autonomic nervous system, and the immune-kynurenine pathway in the etiology of depression. *Curr. Neuropharmacol* 14(7), 665-673 (2016).
- Jeon SW, Kim YK. Neuroinflammation and cytokine abnormality in major depression: cause or consequence in that illness. *World. J. Psychiatr* 6(3), 283-293 (2016).
- Zhuo C, Zhu J, Wang C, et al. Different spatial patterns of brain atrophy and global functional connectivity impairments in major depressive disorder. *Brain. Imaging. Behav* (2016).
- Maes M, Mihaylova I, Kubera M, et al. Activation of cell-mediated immunity in depression: association with inflammation, melancholia, clinical staging and the fatigue and somatic symptom cluster of depression. *Neuropsychopharmacol. Biol. Psychiatry* 36(1), 169-175 (2012).
- Nazimek K, Strobel S, Bryniarski P, et al. The role of macrophages in anti-inflammatory activity of antidepressant drugs. *Immunology* S0171-2985(16), 30320-30325 (2016).
- Curzytek K, Kubera M, Majewska-Szczepanik M, et al. Inhibitory effect of antidepressant drugs on contact hypersensitivity reaction is connected with their suppressive effect on NKT and CD8⁺T cells but not on TCR delta T cells. *Int. Immunopharmacol* 28(2), 1091-1096 (2015).
- Hannestad J, DellaGioia N, Bloch M. The effects of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. *Neuropsychopharmacology* 36(12), 2452-2459 (2011).
- Durairaj H, Steury MD, Parameswaran N. Paroxetine differentially modulates LPS-induced TNF α and IL-6 production in mouse macrophages. *Int. Immunopharmacol* 25(2), 485-492 (2015).
- Ramirez K, Sheridan JF. Antidepressant imipramine diminishes stress-induced inflammation in the periphery and central nervous system and related anxiety- and depressive-like behaviors. *Brain. Behav. Immun* 57(1), 293-303 (2016).
- Martino M, Rocchi G, Escelsior A, et al. Immunomodulation Mechanism of Antidepressants: Interactions between Serotonin/Norepinephrine Balance and Th1/Th2 Balance. *Curr. Neuropharmacol* 10(2), 97-123(2012).
- Tynan RJ, Weidenhofer J, Hinwood M, et al. A comparative examination of the anti-inflammatory effects of SSRI and SNRI antidepressants on LPS stimulated microglia. *Brain. Behav. Immun* 26(3), 469-479 (2012).
- Di Rosso ME, Palumbo ML, Genaro AM. Immunomodulatory effects of fluoxetine: a new potential pharmacological action for a classic antidepressant drug? *Pharmacol. Res* 109(1), 101-107 (2016).
- Dahl J, Ormstad H, Aass HCD, et al. Recovery from major depressive disorder episode after nonpharmacological treatment is associated with normalized cytokine levels. *Acta. Psychiatr. Scand* 134(1), 40-47 (2016).
- Elenkov, IJ. Neurohormonal-cytokine interactions: implications for inflammation, common human diseases and well-being. *Neurochem. Int* 52(1-2), 40-51 (2008)
- Dell'osso L, Carmassi C, Mucci F, et al. Depression, serotonin and tryptophan. *Curr. Pharm. Des* 22(8), 949-954 (2016).
- Toben C, Baune BT. An act of balance between adaptive and maladaptive immunity in depression: a role for T lymphocytes. *J. Neuroimmun. pharmacol* 10(4), 595-609 (2015).
- Levite, M. Neurotransmitters activate T-cells and elicit crucial functions via neurotransmitter receptors. *Curr. Opin. Pharmacol* 8(4), 460-471 (2008).
- Munzer A, Sack U, Mergl R, et al. Impact of antidepressants on cytokine production of depressed patients in vitro. *Toxins (Basel)* 5(11), 2227-2240 (2013).
- Ho PS, Yeh YW, Huang SY, et al. A shift toward T helper 2 responses and an increase in modulators of innate immunity in depressed patients treated with escitalopram. *Psychoneuroendocrinology* 53(1), 246-255 (2015).
- Horowitz MA, Wertz J, Zhu D, et al. Antidepressant compounds can be both pro- and anti-inflammatory in human hippocampal cells. *Int. J. Neuropsychopharmacol* 18(3), pyu076 (2014).
- Thomas J, Khanam R, Vohora D. Augmentation of antidepressant effects of venlafaxine by agomelatine in mice are independent of kynurenine pathway. *Neurochem. Int* 99(1), 103-109 (2016).
- Tsai JH, Kuo CH, Yang P, et al. Effects of antidepressants on IP-10 production in LPS-activated THP-1 human monocytes. *Int. J. Mol. Sci* 15(8), 13223-13235 (2014).