Immunology beyond a textbook: Psychoneuroimmunology and its clinical relevance for psychological stress and depression

Adrian YS Lee
Fourth Year Medicine (Honours)
University of Tasmania

In his fourth year of medicine at the University of Tasmania, Adrian is currently an Honours research candidate. His general and research interests encompass molecular and cellular immunobiology, clinical immunology, medical education and infection control. The primary aim of writing this article was to show how basic immunology can form the basis of many clinical encounters.

Our medical studies encompass many areas of medical science, and immunology is an example of just one. Traditionally, we have been taught that our immune system exists to protect us from pathogens; however, in recent years, this romantic view of the immune system has been challenged and it is now well recognised that it is also involved in whole-body homeostasis and cross talks to other regulating systems of the body. This is the notion of psychoneuroimmunology (PNI). This text will briefly review the current understanding of PNI and how it features prominently in clinical practice as a part of the 'whole person' model of patient care and, especially, in terms of stress and depression. With this in mind, PNI is an emerging medical discipline that warrants integration and consideration in future medical care and practice.

Introduction

At first glance, immunology may be viewed by some as an esoteric medical science that simply provides us with the molecular and cellular mechanisms of disease and immunity. It is a subject that all medical students have to face and no doubt can find quite challenging as well. Yet, in recent times, its role in helping us understand mental health and why individuals behave in certain ways has become increasingly appreciated. [1,2] The novel area of study that attempts to explain this intricate and convoluted relationship between the mind, behaviour, nervous system, endocrine system and finally the immune system is, quite appropriately, termed psychoneuroimmunology (PNI) or sometimes psychoendoneuroimmunology. [3] This was probably something that was never mentioned during our studies because it is quite radical and somewhat ambiguous. So what, then, is PNI all about and why is it important?

Many of us may have come across patients that epitomise the association between mental disturbances and physical manifestations of disease. Indeed, it is this biopsychosocial model that is well documented and instilled into the minds of medical students. [4-7] The mechanism behind this, although something best left to science, is nonetheless interesting to know and appreciate as medical students. This is PNI.

The basic science of psychoneuroimmunology

History

The notion that behaviour and the manifestation of disease were linked was probably first raised by Galen (129-199 AD) who noticed that melancholic women were more likely to develop breast cancer than sanguine women. [8] The modern push for PNI probably began in the 1920s to 1930s when Metal'nikof and colleagues conducted several preliminary experiments in various animals showing that the immune system can be classically conditioned. [9] New interest in this area was established by Solomon *et al.* who, in 1964, coined the term 'psychoimmunology' [10]; however, the concept of PNI was firmly established by the American behavioural scientist Dr Robert Ader in his revolutionary 1981 book, 'Psychoneuroimmunology.' This book described the dynamic molecular and clinical manifestations of PNI through various early experiments. [11,12] In one initial experiment, Ader and fellow researchers successfully demonstrated that the immune system can be conditioned, similarly to Metal'nikov. After pairing saccharin with the immunosuppressive agent,

cyclophosphamide, and administering this to some rats, they found that saccharin administration alone, at a later date, was able to induce an immunosuppressive state marked by reduced titres of haemagglutinating antibodies to injected sheep erythrocytes. [13] The authors postulated that non-specific stress associated with the conditioning process would have elicited such a result. By extension and based on earlier research, [14] the authors believed psychological, emotional or physical stress probably act through hypothalamic pathways to induce immunomodulation which manifests itself in various ways. [13]

Stress, depression and PNI

A prominent aspect of PNI focuses on the bi-directional relationship between the immune system and stress and depression, where one affects the other. [4,15] The precise mechanisms are complicated but are ultimately characterised by the stress-induced dysregulation, (either activation or depression), of the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes. [16] Because of the pleiotropic effects of these hormones, they can induce a dysfunctioning immune system partly through modulating the concentration of certain cytokines in the blood. [15] Endocrine and autonomic pathways upregulate pro-inflammatory cytokines (such as interleukin (IL)-1β, IL-6 and tumour necrosis factor-α (TNF-α)) that can exert their effects at the brain through direct (i.e., circumventricular organs) and indirect access ports (via afferent nerve fibres). [17,18] Such pro-inflammatory cytokines therefore stimulate the HPA axis and activate it leading to the rapid production of corticotropin-releasing hormone. [19-21] Eventually, cortisol is produced which, in turn, suppresses the pro-inflammatory cytokines. Interestingly, receptors for these cytokines have also been found on the pituitary and adrenal glands, thereby serving the ability to integrate neuroendocrine signals at all three levels of the HPA axis. [21,22] Cortisol also has significant effects on mood, behaviour and cognition. On a short-term basis, it may be beneficial; making an animal more alert and responsive. However, increased periods of elevation may give rise to impaired cognition, fatigue and apathy. [23]

In the brain, an active role is played by the once-thought insignificant glial cells which participate at the so-called tripartite synapse (glial cell plus pre- and post-synaptic neurons). [24] It is this unit that is fundamental to much of the central nervous system activity of the PNI system. Pro-inflammatory cytokines like interferon (IFN)-α and IL-1β released from peripheral and central (microglia and astrocytes) sources can alter dopaminergic signals, basal ganglial circuitry, hippocampal

functioning and so on. Consequently, this induces behavioural changes of anhedonia, memory impairment and other similar behaviours. [18,25] Since IFN-α receptors have been found on microglia in the brain, [26] IFN-α likely also causes further local inflammation and further disruption of dopaminergic signals. Excessively activated microglia by a range of inflammatory cytokines can therefore cause direct neurotoxicity and neuropathology. [27] Additionally, these cytokines can induce activity of the indoleamine 2,3-dioxygenase enzyme (found in astrocytes and microglia) which metabolise the precursor of serotonin, tryptophan. The result is a reduction of serotonin and the production of various products, including quinolinic acid, an NMDA (N-methyl-D-aspartate) receptor agonist which leads to excess glutamate and neurodegeneration. These mechanisms are postulated to contribute to the pathogenesis of depression; however, the precise mechanisms of which are yet to be fully elucidated. [28-30]

Recent research into behavioural epigenetics has also provided an additional interesting link whereby stressors to the psychosocial environment can modulate gene expression within the neuroimmune, physiological and behavioural internal environments. This may account for the long-term aforementioned changes in immune function. [31]

Depression has also been shown to activate the HPA and SAM axes as well through inflammatory processes, [28,32] which in turn exacerbates any pre-existing depressive behaviours. [33] This inflammatory theory of depression sheds light onto the complicated pathophysiology of depression, adding to the already well-characterised theory of serotonergic neurotransmission deficiency. [28,33] Interestingly, pro-inflammatory cytokines have been shown to modulate serotonergic activity in the brain as well, [34,35] which provides further insight into this complex disorder. There is question as to whether or not this may have its roots with evolution where the body diverts energy resources away from other areas to the immune system for the promotion of anti-pathogenic activity during stress and depression. [17] For instance, with threat of an injury or wound in an acute situation (the stressor), cortisol (a natural immunosuppressant) would be released via the HPA axis. This aids in energy conservation which in turn, and paradoxically, attempts to minimise the non-helpful effect of immunosuppression in times of infection risks. [17] Depressive behaviour such as lethargy has also been said to have stemmed from the need to conserve energy to promote fever and inflammation. [2] Ultimately, the evolutionary aspects of PNI are under current speculation and investigation to elicit the precise links and relationships. [36]

The alterations of the immune system in stress and depression have implications for other areas of medicine as well. Though conclusive clinical experiments are lacking, it has been strongly hypothesised that this imbalanced immune state can contribute to a plethora of medical ailments. Depression, characterised by a general pro-inflammatory state with oxidative and nitrosative stress, [33,37] can contribute to poor wound healing; and exacerbate chronic infections and pain. [38,39] Stress similarly entails a dysregulated immune system and may contribute to the aforementioned conditions plus cardiovascular disease and minor infectious diseases such as the common cold. [40-44] The link with cancer is somewhat more controversial but both may, in some way, predispose to the development of it through numerous mechanisms such as reduced immune surveillance by immune cells (cytotoxic T cells and natural killer cells), general inflammation and genomic instability. [45,46]

Highlighting the bidirectionality of the PNI paradigm, secondary inflammation caused by a myriad of neurological diseases (e.g., Huntington's disease, Alzheimer's disease) and local and systemic disorders (e.g., systemic lupus erythematosus, stroke, cardiovascular disease and diabetes mellitus) may very well contribute to the pathogenesis of co-existing depression. [47] This may account for the close association of depression and such diseases. Underlying neurochemical changes have been observed in many of these diseases—especially the neurological disease examples—and it has been suggested that depression vulnerability is proportional to how well one can 'adapt' to said neurochemical imbalances. [48,49]

Through an immunophysiological point-of-view, these links certainly makes sense; but it is important to note that there could be other confounding factors, such as increased alcohol consumption and other associated behaviours that accompany stress and depression that can contribute to pathology. [50] The question therefore remains as to how much the mind plays in the pathogenesis of physical ailments.

Figure 1 summarises the general PNI model as it relates to stress and depression.

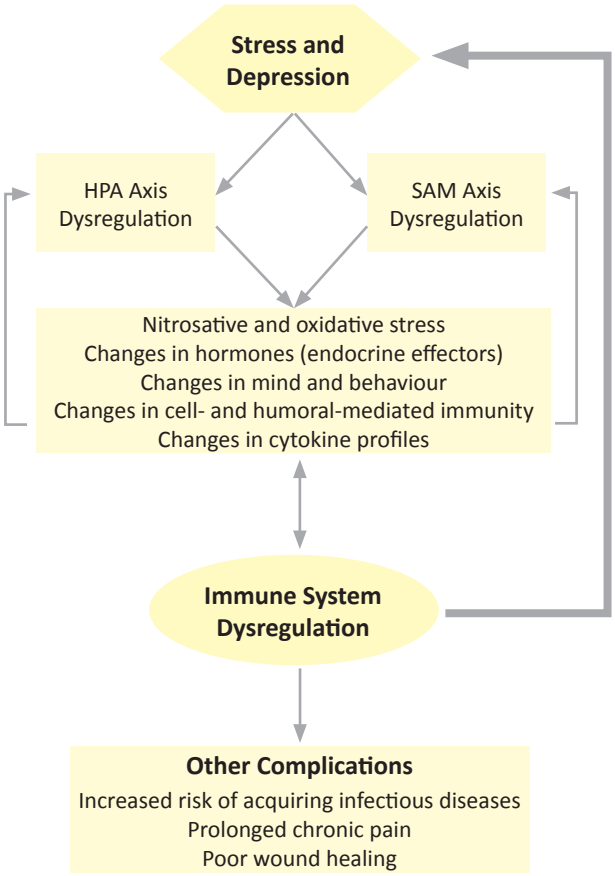

Figure 1. *A summary of the processes involved in stress-induced dysregulation of the immune system and consequences. Note the bi-directional relationship between the immune system and stress/depression. HPA – hypothalamic-pituitary-adrenal; SAM – sympathetic-adrenal-medullary.*

Implications

Having explored the discipline of PNI, what is the importance of this for clinical practice? Because of the links between stress and depression; altered immunity; other ill-effects and behaviour, [3,12] it seems fitting that if we can address a patient's underlying stress or depression, we may be able to improve the course of their illness or prevent, to a certain extent, the onset of certain diseases by correcting immune system dysregulation. [43]

Simply acknowledging the relationship between stress and their role in the pathogenesis, maintenance and susceptibility of diseases is certainly not enough, and healthcare professionals should consider the mental state of mind for every patient that presents before them. It is fortunate, then, that a myriad of simple stress-management strategies could be employed to improve their mental welfare, depending on their individual circumstances. Such strategies include various relaxation techniques, meditation, tai chi, hypnosis and mindfulness practice. These have, importantly, proven cost-effective and lead to self-care and self-efficacy. [51,52]

As an example, mindfulness has received considerable attention in its role of alleviating stress and depression. [52] Defined as the increased awareness and attention to present, moment-to-moment

thoughts and experiences, mindfulness therapy has shown remarkable efficacy in the promotion of positive mental states and quality of life. [52-54] This is particularly important in this age of chronic diseases and their associated unwelcomed psychological consequences. [54] Furthermore, and in light of the discussion above on PNI, there is evidence that mindfulness practice induces physiological responses in brain and immune function. [55,56] This suggests that its benefits are mediated, at least in part, through such positive immunological alterations that modulate disease processes.

With the growing understanding of the cellular and molecular mechanisms behind stress, depression and other similar psychiatric disorders, a host of novel pharmacological interventions to target the previously discussed biological pathways are actively being researched. Most notably is the proposition of the role of anti-inflammatories in ameliorating such conditions where patients present in an increased inflammatory state. This is largely based on experimental work where antagonists to pro-inflammatory cytokines and/or their receptors improve sickness behaviours in animals. [17] As an example, the cholesterol-lowering statins have been found to have intrinsic anti-inflammatory and antioxidant properties. In a study of patients taking statins for cardiovascular disease, it was found that statins had a substantial protective effect on the risk of developing depression. This suggests that the drug acts, at least in part, to decrease systemic inflammatory and oxidative processes that characterise depression. [57] Other drugs being researched aim to tackle additional pathways such as those involving neurotransmitters and their receptors.

Of the neuroendocrine arm of PNI, current research is looking at ways to reverse HPA axis activation. [20] Some tested drugs that act on specific parts of the HPA axis seem to show promise; however, a major problem is tailoring the correct drug to the correct patient, for not all patients will present with the same neuroendocrine profile. [58,59] Neuroendocrine manipulation can also be used to treat or act as an adjunct to other non-HPA axis-mediated diseases. For example, administration of melatonin and IL-2 was able to increase the survival time in patients with certain solid tumours. [60] Needless to say, a great amount of research is further warranted to test and understand possible pharmaceutical agents.

Discussion and Conclusion

The exciting and revolutionary field of PNI has now provided us with the internal links of all the major regulating systems of the human body. The complex interactions that take place is, indeed, a tribute to the complexity of our design, and has provided a basis or mechanism of how our mind and behaviour can influence our physical health. As a result, serious stressors—be them emotional, mental or physical—can wreak havoc on our delicate internal environment and predispose to physical ailments, which can further exacerbate the inciting stressors and our mental state. For said psychological stress or depression, it seems appropriate that if healthcare professionals can ameliorate the severity of these, they may be able to further improve the physical health of an individual. How much so is a matter of debate and further investigation. Conversely, as demonstrated by the bi-directionality model of PNI, addressing or 'fixing' the organic pathology may be conducive to the mental state of patients' minds.

Whilst clinical approaches have been sharply juxtaposed to a very theoretical and scientific review of PNI, this has been deliberately done to hopefully demonstrate how mind-body therapies can exert their physical benefits. Accordingly, valued mind-body therapies deserve as much attention as the scientific study of molecular pharmacology. It is also important to note that even these two approaches (pharmacology and mind-body therapies) are almost certainly the tip of the iceberg; for there is certainly a vast amount more to be further explored in our therapeutic approach to medical conditions. For example, how does a practitioner-patient relationship fit into this grand scheme of things, and how much of a role does it play? No doubt a decent part for sure. Furthermore, whilst the PNI framework provides good foundations for which to explain, (at a basic level), the mechanisms behind the development of stress, depression and associated ailments, further insight is needed into the biological basis of these. For example, a symphony of intricate factors (such as the up-regulation of inflammation-induced enzymes, neurotransmitter changes, dysfunction of intracellular signalling, induced autoimmune activity, neurodegeneration and decreased serum levels of antioxidants and zinc) are at play for the signs and symptoms of depression. [61,62] Thus, the complex pathogenesis of psychological stress and depression begs for further clinical and scientific research into unravelling its mysteries. Nevertheless, with a sound basis behind mindfulness, other similar mind-body therapies and novel pharmacological approaches, it seems suitable for these to be further integrated into primary care [54] and other areas of medicine as an adjuvant to current treatments. If we can achieve this, then medicine undoubtedly has more potent tools in its armamentarium of strategies to address and alleviate the growing burden of chronic disease.

Acknowledgements

My thanks go to Dr E Warnecke and Prof S Pridmore for their support.

Conflicts of interest

None declared.

Correspondence

A Lee: adrian.lee@utas.edu.au

References

[1] Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007;21(2):153-60.
[2] Maier SF. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol Rev. 1998;105(1):83-107.
[3] Ader R, Cohen N, Felten D. Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet. 1995;345(8942):99-103.
[4] Davies J. The relationship between physical and mental illness. A manual of mental health care in general practice. Canberra: Commonwealth Department of Health and Ageing; 2003. p. 151-3.
[5] Eastwood M, Trevelyan M. Relationship between physical and psychiatric disorder. Psychol Med. 1972;2(4):363-72.
[6] Kroenke K, Spitzer RL, Williams JBW, Linzer M, Hahn SR, deGruy FV 3rd, *et al.* Physical symptoms in primary care: predictors of psychiatric disorders and functional impairment. Arch Fam Med. 1994;3(9):774-9.
[7] McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med. 1993;153(18):2093-101.
[8] Marts DF, Murray M, Evans B, Estacio EV. Health psychology: Theory, research and practice. 3rd ed. London: Sage; 2011.
[9] Spector NH. Old and new strategies in the conditioning of immune responses. Ann N Y Acad Sci. 1987;496:522-31.
[10] Solomon GF, Moss RH. Emotions, immunity, and disease: a speculative theoretical integration. Arch Gen Psychiatry. 1964;11:657-74.
[11] Ader R. Psychoneuroimmunology. Surwit RS, Williams RBJ, Shapiro D, editors. Orlando, Florida: Academic Press; 1981.
[12] Ader R. On the development of psychoneuroimmunology. Eur J Pharmacol. 2000;405(1-3):167-76.
[13] Ader R, Cohen N. Behaviorally conditioned immunosuppression. Psychosom Med. 1975;37(4):333-40.
[14] Fessel W. Mental stress, blood proteins, and the hypothalamus: experimental results showing effect of mental stress upon 4S and 19S proteins: speculation that the functional behavior disturbances may be expressions of a general metabolic disorder. Arch Gen Psychiatry. 1962;7(6):427-35.
[15] Glaser R, Rabin B, Chesney M, Cohen S, Natelson B. Stress-induced immunomodulation: implications for infectious diseases? JAMA. 1999;281(24):2268-70.
[16] Yang EV, Glaser R. Stress-induced immunomodulation and the implications for health. Int Immunopharmacol. 2002;2(2-3):315-24.
[17] Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol. 2006;27(1):24-31.
[18] Goshen I, Yirmiya R. Interleukin-1 (IL-1): A central regulator of stress responses. Front Neuroendocrinol. 2009;30(1):30-45.
[19] O'Connor TM, O'Halloran DJ, Shanahan F. The stress response and the hypothalamic-pituitary-adrenal axis: from molecule to melancholia. QJM. 2000;93(6):323-33.
[20] Dunn AJ. Cytokine activation of the HPA axis. Ann N Y Acad Sci. 2000;917:608-17.
[21] Turnbull AV, Rivier C. Regulation of the HPA axis by cytokines. Brain Behav Immun 1995;9(4):253-75.
[22] Silverman MN, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. Viral Immunol. 2005;18(1):41-78.
[23] Erickson K, Drevets W, Schulkin J. Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. Neurosci Biobehav Rev .

2003;27(3):233-46.
[24] Araque A, Parpura V, Sanzgiri RP, Haydon PG. Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci. 1999;22(5):208-15.
[25] Miller AH. Norman Cousins Lecture. Mechanisms of cytokine-induced behavioral changes: psychoneuroimmunology at the translational interface. Brain Behav Immun. 2009;23(2):149-58.
[26] Yamada T, Yamanaka I. Microglial localization of alpha-interferon receptor in human brain tissues. Neurosci Lett. 1995;189(2):73-6.
[27] Hanisch UK. Microglia as a source and target of cytokines. Glia. 2002;40(2):140-55.
[28] Muller N, Schwarz MJ. The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Mol Psychiatry. 2007;12(11):988-1000.
[29] Myint AM, Kim YK. Cytokine-serotonin interaction through IDO: a neurodegeneration hypothesis of depression. Med Hypotheses. 2003;61(5-6):519-25.
[30] Muller N, Schwarz MJ. A psychoneuroimmunological perspective to Emil Kraepelins dichotomy: schizophrenia and major depression as inflammatory CNS disorders. Eur Arch Psychiatry Clin Neurosci. 2008;258 Suppl 2:97-106.
[31] Mathews HL, Janusek LW. Epigenetics and psychoneuroimmunology: mechanisms and models. Brain Behav Immun. 2011;25(1):25-39.
[32] Maes M. Major depression and activation of the inflammatory response system. Adv Exp Med Biol. 1999;461:25-46.
[33] Maes M. The cytokine hypothesis of depression: inflammation, oxidative & nitrosative stress (IO&NS) and leaky gut as new targets for adjunctive treatments in depression. Neuro Endocrinol Lett. 2008;29(3):287-91.
[34] Ramamoorthy S, Ramamoorthy JD, Prasad PD, Bhat GK, Mahesh VB, Leibach FH, *et al.* Regulation of the human serotonin transporter by interleukin-1β. Biochem Biophys Res Commun. 1995;216(2):560-7.
[35] Zhu CB, Blakely RD, Hewlett WA. The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacology. 2006;31(10):2121-31.
[36] Cohen N. The uses and abuses of psychoneuroimmunology: A global overview. Brain Behav Immun. 2006;20(2):99-112.
[37] Maes M. Inflammatory and oxidative and nitrosative stress pathways underpinning chronic fatigue, somatization and psychosomatic symptoms. Curr Opin Psychiatry. 2009;22(1):75-83.
[38] Kiecolt-Glaser JK, Glaser R. Depression and immune function: central pathways to morbidity and mortality. J Psychosom Res. 2002;53(4):873-6.
[39] Fishbain DA, Cutler R, Rosomoff HL, Rosomoff RS. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. Clin J Pain. 1997;13(2):116-37.
[40] Cohen S, Herbert TB. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annu Rev Psychol. 1996;47:113-42.
[41] Cohen S, Tyrrell DA, Smith AP. Psychological stress and susceptibility to the common cold. N Engl J Med. 1991;325(9):606-12.
[42] Chapman CR, Tuckett RP, Song CW. Pain and stress in a systems perspective: reciprocal neural, endocrine, and immune interactions. J Pain. 2008;9(2):122-45.
[43] Godbout JP, Glaser R. Stress-induced immune dysregulation: implications for wound healing, infectious disease and cancer. J Neuroimmune Pharmacol. 2006;1(4):421-7.
[44] Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease JAMA. 2007;298(14):1685-7.
[45] Reiche EM, Morimoto HK, Nunes SM. Stress and depression-induced immune dysfunction: implications for the development and progression of cancer. Int Rev Psychiatry. 2005;17(6):515-27.
[46] Reiche EM, Nunes SO, Morimoto HK. Stress, depression, the immune system, and cancer. Lancet Oncol. 2004;5(10):617-25.
[47] Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. Neuro Endocrinol Lett. 2011;32(1):7-24.
[48] Menza MA, Robertson-Hoffman DE, Bonapace AS. Parkinson's disease and anxiety: Comorbidity with depression. Biol Psychiatry. 1993;34(7):465-70.
[49] Anisman H, Zacharko RM. Depression as a consequence of inadequate neurochemical adaptation in response to stressors. Br J Psychiatry Suppl. 1992(15):36-43.
[50] Cox T. Psychobiological factors in stress and health. In: Fisher S, Reason J, editors. Handbook of life stress, cognition and health. New York: John Wiley & Sons; 1988. p. 603-28.
[51] Chang VY, Palesh O, Caldwell R, Glasgow N, Abramson M, Luskin F, *et al.* The effects of a mindfulness-based stress reduction program on stress, mindfulness self-efficacy, and positive states of mind. Stress Health. 2004;20(3):141-7.
[52] Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. J Psychosom Res. 2004;57(1):35-43.
[53] Brown KW, Ryan RM. The benefits of being present: mindfulness and its role in psychological well-being. J Pers Soc Psychol. 2003;84(4):822-48.
[54] Merkes M. Mindfulness-based stress reduction for people with chronic diseases. Aust J Prim Health. 2010;16(3):200-10.
[55] Davidson RJ, Kabat-Zinn J, Schumacher J, Rosenkranz M, Muller D, Santorelli SF, *et al.* Alterations in brain and immune function produced by mindfulness meditation. Psychosom Med. 2003;65(4):564-70.
[56] Witek-Janusek L, Albuquerque K, Chroniak KR, Chroniak C, Durazo-Arvizu R, Mathews HL. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. Brain Behav Immun. 2008;22(6):969-81.
[57] Stafford L, Berk M. The use of statins after a cardiac intervention is associated with reduced risk of subsequent depression: proof of concept for the inflammatory and oxidative hypotheses of depression? J Clin Psychiatry. 2011;72(9):1229-35.
[58] Thomson F, Craighead M. Innovative approaches for the treatment of depression: targeting the HPA axis. Neurochem Res. 2008;33(4):691-707.
[59] McIsaac SA, Westrin Å, Young AH. Antiglucocorticoids in psychiatry. Adv Psychiatr Treat. 2009;15(4):242-9.
[60] Lissoni P, Brivio F, Fumagalli L, Messina G, Vigore L, Parolini D, *et al.* Neuroimmunomodulation in medical oncology: application of psychoneuroimmunology with subcutaneous low-dose IL-2 and the pineal hormone melatonin in patients with untreatable metastatic solid tumors. Anticancer Res. 2008;28(2B):1377-81.
[61] Leonard B, Maes M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. Neurosci Biobehav Rev. 2012;36(2):764-85.
[62] Capuron L, Miller AH. Immune system to brain signaling: neuropsychopharmacological implications. Pharmacol Ther. 2011;130(2):226-38.