

THE PSYCHO-IMMUNOLOGICAL MODEL AS A PSYCHOSOMATIC ENTITY: A LITERATURE REVIEW OF INTERACTIONS BETWEEN DEPRESSION AND IMMUNITY

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SUMMARY

Background: A large amount of evidence has already shown associations between depression and immunity, a bi-directional relationship seems to be increasingly evident. We showed in several precedent studies that family dynamics (Dubois et al. 2016, Zdanowicz et al. 2015), some coping skills (Manceaux et al. 2016) or gender (Fagniat et al. 2016) are correlated with depression and/or immunity and change the way depression and immunity interact together.

Method: The objective of this review is to study the literature in search of older and recent evidence about how immunity and depression interact and which determinants influence this relationship. We searched on PubMed, PsycINFO, PsycARTICLES and Scencedirect articles with the keywords immunity and depression and with coping, gender and family.

Results and discussions: Surprisingly we observed in the literature that depression is mostly correlated with both inflammatory and impaired immunity mainly for cell-mediated immunity. Recent studies showed that gender differences in immunity seems to explain in part some variabilities concerning depression and acute/chronic stress among men and women. There is evidence for a sexual dimorphism of the immune system. Coping style, perceived control or personality impact the immune system. There is evidence that childhood maltreatment or stress occurring early in life can exert persistent effects over a long period of time like a «biological scar».

Conclusions: There seems to be an individual and biological heterogeneity behind the label of major depressive disorder. We demonstrated the role of several modulators on immunity and depression such as gender, coping, personality, early-life stress or relationships. Many other modulators could exist and should be considered for further investigations.

Key words: depression – immunity – inflammation

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BACKGROUND

A large amount of evidence has already shown associations between depression and immunity, a bi-directional relationship seems to be increasingly evident. Older studies showed variabilities of the immune system among depressive patients suspecting a role of depressive mood on immunity and more recent studies showed that immunity has an impact on the brain, behaviour and mood. We showed in several precedent studies that family dynamics (Dubois et al. 2016, Zdanowicz et al. 2015), some coping skills (Manceaux et al 2016) or gender (Fagniat et al 2016) are correlated with depression and/or immunity and change the way depression and immunity interact together.

METHOD

The objective of this review is to study the literature in search of older and recent evidence about how immunity and depression interact and which determinants influence this relationship. We searched on Pubmed, PsycINFO, PsycARTICLES and Scencedirect articles with the keywords immunity and depression. We especially consider articles concerning mechanisms and external or internal determinants of depression and immunity with the keywords coping, gender, and family. Studies concerning antidepressant or anti-inflam-

matory treatment, patients with cancer, inflammatory disease, infection or other immune system disease are not within our scope. We only consider studies with depressed patients without other diagnosed disease or healthy patients with particular emotional characteristics or disorders.

RESULTS AND DISCUSSIONS

Is Depression a chronic inflammatory disease?

Increased inflammatory biomarkers including cytokines and C-reactive protein (CRP) are observed in peripheral blood of depressed patients (Smith 1991, Maes et al. 1991, 1992, 1995, Anisman 2002). Recent meta-analyses showed significantly increased interleukin-6 (IL-6), interleukin-1 (IL-1), interleukin-2 (IL-2), tumor necrosis factor (TNFa) and CRP (Zorrilla et al 2001; Dowlati et al 2010, Howren et al 2009; Haapakoski et al 2015; Postal et al 2015) in patients with major depressive disorder. Nevertheless there is much evidence for decrease in lymphocytes proliferation and natural killer cell activity (NKCA) in depressive subjects. Two meta-analyses (Herbert and Cohen 1993; Zorrilla et al 2001) found the same general consensus with evidences of decreased counts and activity of helper T cells and suppressor/cytotoxic T cells as well as natural killer cells (NK) among depressed patients compared to healthy controls. An

increase in white blood cells (WBCs) is observed mostly for neutrophils. Surprisingly we observed in the literature that depression is mostly correlated with both inflammatory and impaired immunity mainly for cell-mediated immunity. This result could be contradictory but it seems to be verified that these two parameters can coexist. Zorilla et al (Zorilla et al 2001) showed both a reduced NKCA and an elevated IL-6 and CRP among depressed patients. Pike and Irwin studies' (Pike and Irwin 2006) are consistent with the precedent meta-analysis and showed that decreased serum NKCC (Natural killer cell cytotoxicity) and elevated serum IL-6 were both associated with depression but the elevated IL-6 and decrease NKCC were unrelated to each other. Reduced NKCA in combination with increased serum level of IL6 is indicative of the coexistence of suppression and activation of innate immune response in depression (Blume 2011; Pike and Irwin 2006).

Several studies showed that T cells and cytokines play a pivotal role in both the development and resolution of depression. Evidences suggest that in a context of chronic inflammation as observed in depression, peripheral T cells display maladaptive characteristics (Toben & Baune 2015). It is suggested (Blume et al 2011) that there is an impairment in the switch from the secretion of pro-inflammatory (IFN γ , IL-2) to anti-inflammatory cytokines (IL-10) by T cells and so an increase of T cells CD4+ and decrease of regulatory T cells. It is becoming clear ((Toben and Baune 2015) that T cells are able to enter the central nervous system (CNS) and have multiple roles in immune surveillance, regulation of neurogenic or contribute to maintenance cognition. So in chronic stress or depression T cells could have a maladaptative role in mediating reduced neurogenesis mechanisms. Imbalance between pro-inflammatory and anti-inflammatory factors have a role in overproduction of neurodegenerative metabolites in the brain (Postal et al 2015). On the other hand, cytokines (IL-1, IL-6, TNF α) can cause hypothalamic-pituitary-adrenal axis activation (HPA axis) by stimulating CRF and ACTH. There is evidence in depression and chronic stress for an increased plasma cortisol level due to HPA axis hyperactivity and decreased glucocorticoid receptor sensitivity both in the hypothalamus leading to a dysfunction of the negative feedback and on the immune cells leading to a dysregulation of cell-mediated immunity (Jeon et al 2016). The consequences are an over secretion of CRF, cortisol and pro-inflammatory cytokines and a glucocorticoid resistance (Pariante 2017, Jeon 2016). CRF can create depressive mood, loss of appetite and sleep disturbance (Nemeroff 1996).

Does gender influence immune changes in depression?

It is well known that women are more affected by depression than men. This sex-dependent variability is not entirely understood but is thought to involve gene-

tic, biochemical function of the human brain, hormonal context as well as social factors. Recent studies showed that sex differences in immunity seems to explain in part some variabilities concerning depression and acute/chronic stress among men and women. There is evidence for a sexual dimorphism of the immune system (Pitychoutis et al.). Firstly, the hormonal context is different and indicated to have a crucial role in susceptibility to depression (Kessler et al 2003). Higher risk for depression is observed in women when sex hormones fluctuate (puberty, premenstrual, pregnancy and postpartum) (McCoy et al 2008; Wise et al 2008). Sex hormones appear to be a major candidate in immune alterations in depression even if modulation by sex steroid hormones is complex and far for being elucidated. Estrogens seems to enhance both humoral and cell-mediated immunity while androgens and progestins are immunosuppressive. Low doses of estrogen promote lymphocytes pro-inflammatory responses and high doses promote lymphocytes anti-inflammatory response (Pernis et al 2007). Secondly, it seems that women may be more vulnerable to the central effects of peripheral inflammation. Moieni et al showed that cytokine induction with endotoxin was associated with depressed mood and increased feelings of social disconnectedness in woman only and was not present among woman using hormonal contraceptives. Eisenberger et al. (2009) showed an association between increase IL-6, depressive mood and activity in cortical areas involved in social pain (dorsal anterior cingulate cortex, anterior insula) only in women receiving endotoxin induced-cytokine. Thirdly, Glucocorticoid sensitivity was increased in leukocytes from men and unchanged or even slightly decreased in cells from women. It is therefore possible that following an acute psychosocial stressor, women are exposed for a longer duration, and therefore more susceptible to, the potentially harmful effects of pro-inflammatory processes. Fourthly, studies found a significant reduction of NKCA in depressed men and smaller decreases of NKCA in depressed women (Zorilla et al 2001; Evans et al 1992). In conclusion, Bekhbat et al. (2017) found in a meta-analysis that women display greater behavioural deficits in response to peripheral inflammation (depressed mood, social disconnectedness, activation of social pain circuitry). Women respond to acute stressors in a more inflammatory fashion with an increased mobilization of various immune cells (leukocytosis) and decreased Glucocorticoid sensitivity. Chronic stress is in accord with a greater suppression of cell-mediated immunity.

Role of coping, control and personality on the relationship between depression and immunity

Psychological stressor is perceived, interpreted and evaluated and both a neuroendocrine/immune and emotional/behaviour response emerge. In acute stress, releasing catecholamines promote a fight/flight behaviour. The emotional/behavioural response is influenced by the

subject's specific coping and defense strategies. If efficient coping is not possible with intense or severe prolonged stress the « conservation - withdrawal » or « distress » neuro-endocrine responses are promoted with a hyperactivity of the HPA axis and chronic stress could be appear. People with chronic stress such as burn-out, work-related stress low, caregiver stress, marital problems or bereavement are characterized by decreased proliferative responses of lymphocytes as well as decreased NKCA (Hansel et al 2010; Olf 1999). The way people perceive and manage this stress with their personal resources play a role on this stress impact on the immune system (Picardi et al 2013). So coping style, perceived control or personality impact the immune system. All people do not react in the same way to the same stressors. A lack of personal control has been demonstrated as negatively related to levels of circulating and proliferative lymphocytes (Brosschot et al 1998). Reynaert et al. (1995) showed that NKCA was significantly lower in depressed patients who experienced less subjective control compared to other depressed patients. So an internal locus of control and more subjective control could be a buffer against the decrease in cellular immunity observed in major depression. There is evidence that individuals with active coping strategy to face life events have a better mental health and immune function than people with avoidance or defensive coping style (Olf 1999). Stowel et al demonstrated that the positive or negative effects of coping methods are more evident in high stress conditions (Stowel et al 2001). Koh et al found that a positive reappraisal during a chronic stress period is likely to reverse the stress induced immune response (Koh et al 2006). Shea et al (Shea et al 1993) showed lower immune response among subjects classified as « repressors » of negative affect. Several authors underlined an association between « behavior pattern » and risk for cancer. It is the so called « cancer-prone behavior pattern » (Type C) characterized by anti-emotionality, suppression and inability to express emotions (Baltrusch et al 1991). Relationships have been found between these behavioral factors and immune activity (Baltrusch et al 1991). More recently Caserat et al showed that Higher perceived self-efficacy was significantly associated with lower plasma IL6 concentrations. Manceaux et al showed correlation between immunity, depression and coping strategies. Alexithymia has been described by Sifneos (Sifneos 1973) and is a psychological trait characterized by a difficulty in verbalizing feelings, and by an inaccuracy in identifying and describing emotions. Several studies showed that alexithymia is associated with impaired immune response. There is evidence for lower counts of NK (CD57/16) and cytotoxic lymphocytes (CD8) among men (Dewaraja et al 1997) and women (Todarello et al 1989) with an alexithymia trait. These studies observed an altered function of cell-mediated immunity and of ratios CD4/CD8 (Corcos et al 2003; Guilbaud et al 2003).

Role of psychological stress on the relationship between depression and immunity

Several studies investigate the impact of psychological stress on the immune system and others investigate the impact on depression. So it is known that stress improves depression and immunity but it is more difficult to determine if a psychological stressor influenced the relation, the way that depression and immunity interact because studies involving the two parameters are rare. In other words, our question is whether psychological stress, in addition to its effect on depression and immunity, may influence the way the individual reacts to immune variants and depression. In a previous study Zdanowicz et al showed a cumulative effect between the family relationship in the family of the origin, cellular immunity and the severity of the depression (Zdanowicz et al 2015).

There is evidence that childhood maltreatment or stress occurring early in life can exert persistent effects over long periods of time like a « biological scar » (Pariante et al 2017).

CONCLUSIONS

Surprisingly we observed in the literature that depression is mostly correlated with both inflammatory and impaired immunity mainly for cell-mediated immunity. Firstly, this pattern seems to be verified and it is even the hallmark of depression. We showed in this review the complexity of the immune system. In the same individual an activation could be exist in one part of the immune system and a suppression in an other part. Inflammatory and T cells seems to play an important role. Secondly, it seems to have some « immune heterogeneity » behind the label of major depressive disorder and immune disturbances are not the same for all depressed patients. Third, there is evidence for several modulators which have the capacity to change the relation between immunity and depression. We outlined the role of gender and evidence for a sexual dimorphism of the immune system. Hormonal environment but also the way inflammatory acts on the female brain should be further investigated for better understanding and consistent evidence. There is evidence that individuals with active coping strategy to face life events have a better mental health and immune function than people with avoidance or defensive coping style or with a « repressive » personality such as seen in alexithymia. Evidence concerning links between family relationships and depression are poor and we have only found studies about childhood maltreatment showing that early-life stress or trauma could leave a «biological scar» in adulthood. For further research it would seem interesting to consider the individual and biological heterogeneity but also and especially the many modulators of the relationship between immunity and depression.

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Contribution of individual authors:

All authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data.

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