Treatment failure in major depression associated with chronic inflammation of the immune system: a psychoneuroimmunological hypothesis

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Abbreviations
MDD: Major Depressive Disorder/ CNS: Central Nervous System/ IS: Immune System / IL: Interleukin / AD: Antidepressants / PICs: Pro-inflammatory cytokines/ TCA: Tricyclic Antidepressants/ SSRI: Selective Serotonin Reuptake Inhibitors

ABSTRACT

The pharmacological treatment of major depressive disorder (MDD) fails to respond in 30% to 50% of the cases, triggering researchers to dig deeper into the neurobiological underpinnings of depression. This has put the immune system (IS) in the spotlight and induced the formulation of the "cytokine hypothesis of depression" according to which ―immune response act as neuromodulator that mediate the behavioural and neurobiological features of depression―. **Objective:** In our paper we aim to deepen into the relationship between chronic inflammation of the IS and depression, in order to understand why some people fail to respond to the main pharmacological treatment. **Method:** Application of a systematical research in relevant databases and following the main authors in this particular branch of psychoneuroimmunology. **Results:** Monoamine treatment and IS interact and modify each other, suggesting that the lack of clinical therapeutic benefit of antidepressants (AD) is, somehow, associated with overall activation of the inflammatory system. **Discussion:** Since the current literature demonstrates an association between antidepressant action and cytokine function in MDD, we suggest a new treatment approach merging the actual pharmacological treatment with a behavioural pre-anti-inflammatory treatment in the mindfulness' line that is demonstrated to be able to reduce the chronic inflammation of the IS.

1. Introduction

Major depressive disorder (MDD) is predicted to be the second leading cause of disability by 2020 (Baune, Dannlowski, Domschke, Janssen, Jordan, Ohrmann, *et al.* 2010; Powell, Smith, Hackinger, Schalkwyk, Uher, McGuffi, *et al.* 2012). Lifetime prevalence rates of major depression are estimated to be 20% in women and about 10% in men (Steffens *et al.* 2000, *cfr.* Irwin 2002). Depression predicts mortality whether it is considered for many authors as a disorder or treated as a continuous risk factor (*cfr.* Irwin

2002). The factors that contribute to the more chronic nature of depression are not entirely known although the presence of chronic disease, exposure to stressful life events and personal losses, diminished social supports, and declines in self-concepts of efficacy and mastery are suggested (Blazer, 1989, *cfr.* Irwin 2002). Although monoamine-pathway targeted AD are the main treatment choice, two-thirds of patients fail to respond to the first AD prescribed and the remaining third fails to respond to multiple AD treatments (Miller, Maletic, and Raison, 2009; Powell, *et al.* 2012).

The insufficiency of the monoamine hypothesis to explain several aspects of mood regulation has resulted in an expanded search for the neurobiological underpinnings of depression (Anders, Tanaka and Kinney, 2013). Numerous researches have been interested in the role of the IS the in etiology, course and treatment of MDD (Maier and Watkins, 1998; Irwin, 2002; Irwin and Miller, 2007; Leonard and Myint, 2009; Miller, et al, 2009; Janssen, Caniato, Verster and Baune, 2010).

Maes *et al.* (1993, *cfr.* Maes, Berk, Goehler, Song, Anderson, *et al.* 2012) hypothesized about the bidirectional communication and the relationship that both immune and central nervous system (CNS) hold. It is now generally accepted that immune dysregulation plays an important role in the pathogenesis of major depression (Gold and Irwin 2006, *cfr.* Janssen *et al.* 2010). The role of the immune-activated inflammatory cytokines has been identified as a key area of focus in understanding the neurobiological pathways that trigger depressive states (Janssen *et al.* 2010; Anders, *et al.* 2013). The term cytokine encompasses a large and diverse family of signalling molecules that primarily gave immune modulating activity and that are produced widely throughout the body by cells of diverse embryological origin. Cytokines are primarily protein peptides or glycoproteins, used extensively in immune modulation, secreted by a wide variety of cells in the IS, which play a role in the pathogenesis of numerous disorders including infection, autoimmune disease, stroke and even depression. Traditionally they can be classed as lymphokines, interleukins (IL), and chemokines, depending on their presumed function, target, or cells of origin (Janssen *et al.* 2010).

Increased levels of pro-inflammatory cytokines (PICs) have been repeatedly observed in depressed individuals prompting the formulation of the "Cytokine hypothesis of depression" (Anders *et al.* 2013).

The cytokines-depression hypothesis postulates that AD may prevent the onset of sickness behaviour by modulating PICs (Janssen *et al.* 2010). While there are good evidences which suggest that inflammation can contribute to the development of depression it is less evident that blocking inflammation will lead to a reduction of depressive symptoms or be efficacious in treatment-resistant depression (Jones and Thomsen, 2013). Existing data indicates that inflammatory biomarkers may identify depressed patients who are less likely to respond to conventional AD treatment (Miller *et al.* 2009) which may be also relevant to the potential clinical applications of the association between inflammation and depression.

One of the firsts in hypothesize about the shared pathways between the IS and the CNS were Maier and Watkins in 1998, in their article "Cytokines for Psychologists: Implications of Bidirectional Immune-to-Brain Communication for Understanding Behaviour, Mood and Cognition" in

which they described how PICs are known to mediate in a behavioural complex induced by infection and immune trauma called "Sickness Behaviour" (Maier and Watkins, 1998; Anders *et al.* 2013). Sickness behaviour is characterized by somatic, cognitive, and behavioural changes, such as fever, weakness, malaise, and impaired concentration (Hart 1988, *cfr.* Anders, *et al.* 2013), it has an evident similarity with clinical depression. The first inkling that there are phenomenological similarities between those two conditions may share common pathways, that is, activation of the inflammatory responses system was published in 1993 (*cfr.* Myers, 2008; Maes *et al.* 2012).

Therefore, in this paper we aim to clarify how some specific molecules of the IS (cytokines) interact with AD, and how this interaction affects the efficacy of the pharmacological treatment in MDD. We will also attempt to analyse an alternative treatment for depression which is based on the belief that improving the inflammatory state of the IS will, somehow, alleviate depression symptoms. We hope our research pathway will guide future research efforts in depression and AD treatment response.

2. Method

We have built a systematic review of the pubmed, psychinfo, pubpsych and the UAB library's catalog "el trobador +" databases with articles published between 2004 and 2015. We have also searched in the first reviewed articles' bibliography in order to select those we found more interesting. With an exception for articles that are the bases for knowledge in psychoneuroimmunology and its relation with depression, such as the Maier and Watkins' article which was written in 1998, and the review made by Irwin in 2001. The searches applied in the databases were Psychoneuroimmunology AND depression AND treatment failure, and also, Psychoneuroimmunology AND depression AND cytokines AND antidepressants. We have finally used 45 reviews or meta-analysis, all of them in English.

3. Linkage between the immune system and depression

3.1. *Depression*

Depressive syndromes and major depression are exceedingly common, and they are a chronic and recurrent disorder with residual disability. Nearly one in four women and one in six men experience depression during their lifetime (Kessler *et al.* 2010, *cfr.* Slavich and Irwin, 2014). In fact, depression has been estimated to be the fourth leading cause of overall disease burden and the leading cause of nonfatal disease burden worldwide (Üstün *et al.* 2004, *cfr.* Slavich and Irwin, 2014), and in primary care outpatients, point prevalence rates ranges from 9% to 20% for all depressive disorders (Barry *et al.* 1998, *cfr.* Irwin, 2002). The factors that contribute to the more chronic nature of depression are not fully known, although the presence of chronic disease, exposure to stressful life events and personal losses, diminished social supports, and declines in self-concepts of efficacy and mastery are suggested (Blazer, 1989, *cfr.* Irwin, 2002).

Less is known about the effects of major depression on the outcomes of other diseases and whether depression alters the onset and progression of chronic medical disorders such as infectious disease and/or inflammatory disorders (Irwin, 2002). There is now substantial evidence that psychological stress can trigger significant increases in inflammatory activity (*i.e.* in the

absence of physical injury; Glaser and Kiecolt-Glaser, 2005, *cfr.* Slavich and Irwin, 2014). Increases in inflammation can in turn elicit profound changes in behaviour, which include the initiation of depressive symptoms such as sad mood, anhedonia, fatigue, psychomotor retardation, social-behavioural withdrawal (Slavich and Irwin, 2014). These somatic, cognitive and behavioural changes caused by PICs have been defined by many authors as sickness behaviour (we will delve into it later on this paper) and it represents an organized strategy for fighting infection by conserving metabolic resources and helping individual avoid further stressors (Anders *et al.* 2013). If it is substantiated that biobehavioural factors impact immune related diseases, then it is equally important to know whether interventions that influence psychological adaptation can have attendant effects on immunological and health status outcomes (Irwin, 2002).

The mechanisms that count for this relationship between depression and progression of immune-related disorders were treated with special attention in Irwin's paper (2002). There are few fundamental pathways by which cytokines may contribute to depression, they have been shown to access into the brain and interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function, and neural plasticity (Dantzer, O'Connor, Freund, Johnson and Kelly, 2008; Raison et al,. 2006, *cfr.* Miller *et al.* 2009).

It remains unclear whether activation of inflammatory pathways in the CNS during depression originates primarily in the periphery and/or whether stress or other yet to be identified processes induce inflammatory directly within the brain (Miller *et al.* 2009).

3.2. *Understanding depression*

For more than half a century, efforts to understand the neurobiological underpinnings of depression have been dominated by the view of many authors that depression is caused by a deficiency in synaptic concentrations of monoaminergic neurotransmitters, including serotonin and norepinephrine (Anders *et al.* 2013). This idea has been called the monoamine hypothesis and has become the basis for most of the treatments in the market. However, the efficacy of AD drugs based on the fundamental premise of the monoamine hypothesis has been limited, with estimates between 30% and 50% of individuals treated with AD medication not showing adequate response (Schatzberg, 2000, *cfr.* Anders *et al.* 2013).

The credibility of the monoamine theory and the therapeutic efficacy of these compounds in the treatment of depression have been extensively criticized, and in many instances the evidence used to support these criticisms is found to be weak (Walker, 2013). Research on the IS and its role in the etiology of depression has emerged as an especially promising area for study, in particular, the role of immune-activated inflammatory cytokines, a key area of focus in understanding the neurobiological pathways that trigger depressive states by way of direct and indirect effects on hypothalamic-pituitary-adrenal (HPA) axis, and by altering monoamine neurotransmitters in multiple regions of the brain (Anders *et al.* 2013).

3.3. *Sickness Behaviour*

When infection or injury occurs, PICs are responsible of orchestrating the early immune response, including sickness behaviour, characterized by somatic, cognitive, and behavioural

changes, such as fever, weakness, malaise, listlessness, hyperalgesia, and impaired concentration, represents an organized strategy for fighting infection by conserving metabolic resources and helping an individual avoid further stressors (Anders *et al.* 2013).

According to Dantzer (2001, 2009) sickness behaviour is an expression of a biologically-mediated motivational state triggered by the innate IS that resets an organism's priorities to adaptively cope with the threat of bodily insult. The costs of shifting resources and priorities during this state are purportedly offset by the critical advantages offered for fighting infection (Dantzer 2001, 2009; Anders *et al.* 2013).

Comparing both, clinical depression and sickness behaviour it is easy to find a clear similarity (Maes *et al.* 2012). For example, similar to sickness behaviour, symptoms of depression such as anhedonia, fatigue, hypersomnia, anorexia and psychomotor retardation (*i.e.* slowed speech, thinking, and body movements) all tend to reduce activity and encourage rest, thereby conserving energy. Although there are many similarities, there are also significant differences such as the length of course, the variety of symptoms or the mood. Therefore, we conclude that this may be evidence that PICs are involved in depression, since physical symptomatology is equivalent to sickness behaviour (Anders *et al.* 2013).

3.4. Role of inflammation in depression. A particular focus on pro-inflammatory cytokines

Numerous associations have been observed between depression and IS in recent years (Musselman *et al.* 1998, *cfr.* Irwin 2002). Psychological and physical stressors increase the release of PICs and alter expression of adhesion molecules. For example, Appels et al. (2000) have found that angioplasty patients with feelings of exhaustion and depression have higher levels of IL-1 and TNF (*cfr.* Irwin, 2002).

Increased levels of PICs have been repeatedly observed by lots of authors in depressed individuals, prompting formulation of the "macrophage theory of depression" (Smith, 1991, *cfr.* Anders *et al.* 2013), and its successive formulation as the 'cytokine hypothesis of depression' (Anders *et al.* 2013). According to the cytokine hypothesis, PICs produced by macrophages during the acute phase of an immune response act as neuromodulators that mediate the behavioural and neurobiological features of depression (Anders *et al.* 2013).

Cytokines are the key mediator of inflammation; therefore they can alter neurochemical and neuroendocrine processes that have wide-ranging effects on physiology and behaviour. This review focuses primarily on PICs IL-1, IL-6, and TNF-α, which together coordinate a variety of cell functions that stimulate and enhance inflammation. For example, they promote the differentiation of lymphocytes called cytotoxic T cells, which kill pathogens that are introduced into the body during physical wounding (*cfr.* Slavich and Irwing, 2014).

Inflammatory cytokines also promote increased vascular permeability and cellular adhesion, which allows immune cells to leave the blood vessels (*i.e.* the "boulevards") and migrate to tissues (*i.e.* the "battlefields") where they can neutralize or eliminate pathogens (Dhabhar *et al. cfr.* Slavich and Irwin 2014). Chemokines (a family of small cytokines) are activated by the PICs TNF-α, IL-6, and IL-1, and they continually survey the body to screen for pathogens in a process called immunosurveillance. Once a pathogen

or infection has been identified, chemokines can act as chemoattractants that recruit other immune cells to the site of inflammatory activity (Murphy, 2011, *cfr.* Slavich and Irwin, 2014).

3.5. *Inflammation: Friend and Foe*

Down-regulating the response once a pathogen has been cleared is, according to Kushner (1982) and Medzhitov (2008) critical to resolve infection, repair tissue damage, and return the body to a state of homeostasis (*cfr.* Slavich and Irwin, 2014). An altered or prolonged response can actually cause more damage to a host than the pathogen itself (Barton, 2008, *cfr.* Slavich and Irwin, 2014). Indeed, it is now widely recognized that chronic inflammation plays a role in several major diseases including asthma, arthritis, diabetes, obesity, atherosclerosis, certain cancers, and Alzheimer's disease (Couzin-Frankel, 2010, *cfr.* Slavich and Irwin, 2014). And according to Segerstrom and Miller, (2004) and Steptoe *et al.* (2007), one factor that can alter the adaptive response of innate IS and prolong inflammation is stress.

But how does the immune and nervous system communicate in order to orchestrate such a diverse pattern of changes? Quoting Maier and Watkins (1998):

> *"The most obvious possibility is that cytokines travel to the brain in the bloodstream and cross the blood-brain barrier. This pathway is credible considering that there are specific receptors for IL-1, IL-6 and TNF in the brain and neurons. Also blocking IL-1 receptors in the brain can prevent some of the sickness responses to peripheral administration of cytokines and that the administration of IL-1 directly to the brain produces many of the sickness responses (p. 88)."*

But as cytokines are large lipophobic molecules they are not likely to cross the blood-brain barrier and enter the brain. Numerous investigations proposed different specialized mechanisms such as active transport, weak brain-barrier areas, and receptor inside the blood vessels may allow cytokines access to the brain; however it does not seem to be sufficient to produce psychological changes (*cfr.* Maier and Watkins, 1998). According to Maier and Watkins (1998) there are alternative communication pathways between the brain and the IS. The CNS receives neural and humoral signals about the peripheral inflammatory response thought PIC-induced activation of afferent vagal signals, effects of TNF-α at the sensory nuclei of the solitary tract, and all three PICs entering the brain through the different mechanisms prior mentioned (Maes *et al.* 2012) affecting hypothalamus, and hippocampus. This is where the neural cascade begins which result in individual responses that are known as sickness (Maier and Watkins, 1998). The most pronounced changes are in norepinephrine and serotonin release and action (Linthorst *et al. cfr.* Maier and Watkins 1998). We will talk about the importance of these monoamine responses later on this paper.

So far we have shown different hypothesis undergoing the etiology of MDD, such as the monoaminergic hypothesis or the cytokine-based hypothesis, but none of these can completely explain the variety of symptoms of this heterogeneous disorder. We have also observed how the IS talks to the brain through different pathways affecting the brain and causing behavioural changes. Next we will explain the exact pathways by

which cytokines are believed to orchestrate such a diverse pattern of changes.

4. Synergic relationship between cytokines and CNS

The efforts to understand the neurobiological underpinnings of depression have been dominated by the view that depression is caused by a deficiency in synaptic concentrations of monoaminergic neurotransmitters including serotonin and norepinephrine (Anders *et al.* 2013). This belief is known as "monoaminergic hypothesis of depression". The majority of currently used AD drugs act on the monoamine serotonin neurotransmitter systems (Roman, Kreiner and Nalepa, 2013), and the prescription of selective serotonin reuptake inhibitors (SSRIs) is a major component in the medical treatment of mood related psychopathology (Walker, 2013).

The efficacy of these AD drugs based on the fundamental premise of the monoamine hypothesis has been limited, especially because it is estimated that between 30% and 50% of individual treated with AD medication do not show adequate response (Schatzberg, 2000 *cfr*. Anders *et al.* 2013). It is now clear that this hypothesis by itself does not answer all the questions about the etiology of depression due to the lack of therapeutic efficacy of its treatment.

Lots of hypothesis has been made since the SSRIs launching in 1972 but it is now obvious that cytokines play an important role in the etiology of mood-related disorders. They can exert direct and indirect effects on brain function through their influence on neurotransmitter, neurogenesis and the HPA axis influencing neuroplastic changes relevant to depression (Bauer, Papadopoulos, Poon, Perks, Lightman, Checkley, and Shanks, 2003; Eyre and Baune, 2012; Mills, Scott, Wray, Cohen-Woods and Baune, 2013; Felger and Lotrich, 2013).

The evidence for inflammatory changes in the brain in depression suggests that an increase in inflammation-induced apoptosis, together with a reduction in the synthesis of neurotrophic factors caused by a rise in brain glucocorticoids, may also play a role in the pathology of these disorders. If this is the case, it is expected that the more severe cases of depression —those who are resistant to AD treatment— present higher inflammatory disturbance (Carvalho, Torre, Papadopoulus, Poon, Juruena, Markopoulu, *et al.* 2012).

In order to define treatment resistance we will use Sackeim's (2001) definition: resistance to a given treatment is concluded if, despite continued adherence to the same medication and dosage that produced an initial response, a patient experienced relapse or recurrence of a depressive episode. There is also the Thase and Rush (1997) staging criteria, which recognises five stages of treatment-resistance according to the number of treatment trials adequately delivered (Carvalho *et al.* 2012). Their data support the hypothesis that lack of clinical therapeutic benefit of AD is associated with further immunological impairment in the presence of a concomitant HPA axis disturbance, and more importantly biomarkers may be able to identify patients who may benefit from early access to adjuvant therapies.

Of note, the main inflammatory cytokines that appear elevated in depressive states are IL-6 and TNF-α, which also have been found to be increased in treatment-resistant patients, compared to patients who would later respond to AD (Carvalho *et al.* 2012;

Dunjic-Kostic *et al.* 2012; O'Brien, 2007 *cfr.* Janssen *et al.* 2010).

4.1. Undergoing specific effects of PICs on depressive-related pathways

According to Miller et al. (2009) numerous studies have interest in fundamental pathways by which cytokines may contribute to depression. Cytokine have been shown to access the brain and interact with virtually every pathophysiologic domain relevant to depression, including neurotransmitter metabolism, neuroendocrine function and neural plasticity.

4.1.1. *Neurotransmitters.*

Once cytokine reach the brain, they have the capacity to influence the synthesis, release and reuptake of mood-relevant neurotransmitters, including monoamines (Miller, 2008 *cfr.* Miller *et al.* 2009) such as, serotonin, norepinephrine, and dopamine.

Serotonin (5-HT). The 5-HT system is undoubtedly one of the most studied neurotransmitter systems in depression, and SSRIs are the most widely prescribed AD medication (Hernandez, Mendieta, Pérez-Tapia, Bojalil, Estrada-Garcia, Estrada-Parra *et al.* 2009; Walker, 2013; Felger and Lotrich, 2013). Many aspects of the 5-HT system are altered in major depression, including changes in 5-HT turnover, and receptor and transporter binding (Felger and Lotrich, 2013).

The PICs affect 5-HT metabolism by reducing tryptophan (TRP) —the primary aminoacid precursor of serotonin— levels (Miller *et al.* 2009). Cytokines can activate IDO, an enzyme which metabolizes TRP, thereby reducing serotonin levels (Miller *et al.* 2009; Janssen *et al.* 2010; Roman *et al.* 2013). Furthermore, inflammatory cytokines, such as IL-1β, may reduce extracellular 5-HT levels, via activation of the serotonin transporter mechanisms (Janssen *et al.* 2010). Although alterations in 5-HT metabolism may not be the primary mediator of many behavioural symptoms resulting from cytokine-induced IDO activity (Dantzer *et al.* 2011; Maes *et al.* 2010), the 5-HT transporter (5-HTT) may serve as a biological substrate by which cytokines can affect 5-HT neurotransmission and subsequently behaviour (Miller *et al.* 2009; Felger and Lotrich, 2013).

Dopamine (DA). Cytokines also have been shown to influence the synthesis of DA and reduce its availability in relevant brain regions (Miller *et al.* 2009). Numerous studies mentioned in Felger and Lotrich (2013) (such as Willner, 1983; Capuron *et al.* 2001, 2009; Dunlop and Nemeroff, 2007; Majer *et al.* 2008; Stein, 2008; Felger and Miller, 2012), affirm that the fatigue of depression, which is often a residual symptom of SSRI therapy, is a prominent feature of cytokine-induced depression, and may represent cytokine effects on the basal ganglia and DA function. Changes in DA synthesis, release and/or receptor signalling have been proposed as potential mechanisms that may contribute to anhedonic and psychomotor symptoms. Miller et al. (2009) proposed that cytokine-induced effects on the basal ganglia and DA may represent an important mechanism whereby cytokines inhibit behavioural activation.

Glutamate. The efficacy of N-methyl-D-aspartate (NMDA) receptor antagonist drugs, such as ketamine, in rapid AD responses has prompted much attention to the role of glutamate in the pathophysiology of depression (Dowlati *et al.* 2010; Sanacora *et al.* 2012 *cfr.* Felger and Lotrich, 2013). This neurotransmitter mediates the vast majority of excitatory transmission in

the brain and is engaged in cognition and emotion, processes that are commonly affected in depression (Roman *et al.* 2013). According to Bansar *et al.* (2011) and Beumer *et al.* (2012), the signs commonly observed in depression, are related to excessive levels of glutamate and increased glutamatergic neurotransmission (*cfr.* Roman *et al.* 2013). PICs promote the synthesis of the endogenous glutamate receptor agonist quinolinic acid, increase glutamate release and inhibit glutamate re-uptake by astrocytes (Felger and Lotrich, 2013), and by extension may inhibit the release of dopamine (Miller *et al.* 2009) and promote glutamate release through activation of extrasynaptic NMDA receptors (NMDARs) and contributing to glutamate toxicity (Miller *et al.* 2009; Dowlati *et al.* 2010; Hardingham *et al.* 2002, *cfr.* Felger and Lotrich 2013). Moreover, several authors found that the activation of NMDA receptors perpetuates the pro-inflammatory activity of microglia, thus participating in the pathology of depression (Dowlati *et al.* 2010; Roman *et al.* 2013).

4.1.2. *Neuroendocrine system*

HPA axis. In addition to the alterations of neurotransmitter systems, numerous studies claim that PICs contribute to depressive symptoms by activating the hypothalamic-pituitary-adrenal axis (HPA) and inducing glucocorticoid resistance and hypercortisolemia, features commonly observed in depressive states (Leonard 2001; Hernandez *et al.* 2009; Leonard and Myint, 2009; Haroon *et al.* 2012 *cfr.* Roman *et al.* 2013). Backing this idea, the mentioned study of Carvalho *et al.* 2013 supports the hypothesis that the presence of HPA axis distribution accompanying with further immunological impairment may produce the lack of clinical therapeutic benefit of AD.

Roman *et al.* (2013) proposed that inflammatory activation of the IS is perceived and processed by the brain as a stressor and results in corticotropin-releasing hormone (CRH) release from the hypothalamus and subsequent activation of the HPA axis and adrenocorticotropic hormone (ACTH), as well as cortisol, all of which have been found to be elevated in patients with depression (Miller *et al.* 2009; Janssen *et al.* 2010; Anders *et al.* 2013) Moreover, according to Mills et al. (2013) it is plausible that the hyperactivity of the HPA-axis could be a consequence of an elevation in cytokines, attributable to potentially both environmental and genetic moderators.

A pathway by which cytokines seems to influence HPA axis is through effects on negative feedback regulation. Impaired regulation of the HPA axis is reflected by decreased responsiveness to glucocorticoids (Miller *et al.* 2009; Anders *et al.* 2013). On the other hand, glucocorticoids seems to inhibit the production of inflammatory cytokines, however, this inhibition also appears impaired during both acute depressive episodes and in chronic depression (O'Brien *et al.* 2004 *cfr.* Janssen *et al.* 2010; Dowlati *et al.* 2010). Banasr *et al*, (2011 *cfr*. Roman *et al.* 2013) claimed that glucocorticoids also involved glutamate action, perpetuating glutamate toxicity as well as decreasing the synthesis of trophic factors.

Therefore, it is reasonable that HPA-mediated vulnerability to cytokine-induced depression represents a more general hyper-responsiveness and pre-existing vulnerability to stress or inflammatory challenge (Pace *et al.* 2007 *cfr.* Felger and Lotrich, 2013) which may be mediated by alterations in glucocorticoid receptor (GR) expression or function (Miller *et al.* 2009)

4.1.3. *Growth factors.*

Inflammatory cytokines have repeatedly been observed to influence both neuronal development and apoptosis (Roman *et al.* 2013) by significant disturbances in neurogenesis and in the release of neurotrophins, including brain-derived neurotrophic factor (BDNF), underpinning the volumetric changes of brain areas such as hippocampus and prefrontal cortex in depressed individuals (Duman, 1988 *cfr*. Walker, 2013). In fact, both stress and subsequent inflammatory cytokine activity may adversely influence neurogenesis and neuroplasticity (Roman *et al.* 2013).

Miller et al. (2009) claimed that cytokines are important for providing trophic support to neurons and enhance neurogenesis while contributing to normal cognitive functions such as memory. Nevertheless, in the context of prolonged activation, cytokine networks can promote an interconnected suite of abnormalities including diminished neurotrophic support, decreased neurogenesis, and increased glutamatergic activation, oxidative stress, induction of apoptosis and dysregulation of neural interactions and cognitive function.

Indeed, there is now a vast body of compelling evidence that demonstrates BDNF and neurogenesis are significantly impaired in depression and in animal models of depression (Duman, 1998 *cf*r. Walker, 2013).

4.1.4. *Genetics.*

Twin studies have shown that phenotypes depression and increased immune activation are heritable, and that the link between immune activation and depression, at least in part, is due to shared genes regulating immune function and inflammatory response (Bufalino *et al.* 2012). Interactions between immune-cells, monoamine, endocrine system, and neuropeptides seem to be variously related with several functional gene polymorphisms associated with vulnerability to depression or with certain symptom dimensions of this cytokine-induced depression as Felger and Lotrich (2013) highlighted.

By these findings has been raised that specific polymorphisms may be associated with risk for specific sets of symptoms (Felger and Lotrich, 2013). Therefore, identifying inflammatory biomarkers that confer vulnerability to or protection from certain aspects of cytokine-induced depression and may detect patients who are less likely to respond to treatment and provide insight into the potential mechanisms of cytokine effects on behaviour and novel treatment strategies (Felger and Lotrich, 2013; Miller *et al.* 2009).

Felger and Lotrich (2013) found evidence of functional polymorphisms in the promoter region of the IL-6 gene ―the genotype that produces more IL-6― was found to be associated with depression. It's also been reported that a serotonin reuptake promoter polymorphism (5-HTTLPR) was associated with depression but primarily with neurovegetative symptoms and not the more psychological symptoms (Bufalino *et al.* 2013; Felger and Lotrich, 2013). However, two studies found no effect of the 5-HTTLPR polymorphism in IFN-α-induced depression (Kraus *et al.* 2007; Sye *et al.* 2010 *cfr.* Bufalino *et al.* 2013)

Many other polymorphisms on depression-related pathways have been found. For example, a polymorphism from BDNF (Val/Met allele) was associated with the more psychological and cognitive symptoms of depression (Felger and Lotrich, 2013; Miller *et al.* 2009). Also, functional polymorphisms

in genes involved in DA neurotransmission and GR and CRH receptor 1 (Felger and Lotrich, 2013).

4.2. Genetic predisposition to treatment response

Another important variant on the genetics studies in this field of study is the one focused in the relationship between pro- and anti-inflammatory cytokines genes and the efficacy of pharmacological treatment, as a potential use of pharmaco-epigenetic biomarker at the baseline predictors of AD response (Powell *et al.* 2013).

The first genetic study in IL-1B genes (IL1-β-511(C/T)), Yu *et al.* (2003) (*cfr.* Bufalino *et al.* 2013) studied the C-511T polymorphism in a sample of 157 patients with MDD and 112 controls but no significant difference in either genotype or allelic distribution was found between the two groups. However, a subgroup of MDD patients who were homozygous for the "low producer", -511C allele, were found to have higher depressive symptom severity and less favourable response to fluoxetine treatment when compared with -511T carriers. They also found that the C genotype of C-511TSNP, which codes for the IL-1β receptors, was associated with poorer therapy outcome after 4 weeks of AD treatment (Yu *et al.* 2003a, *cfr.* Bufalino *et al.* 2013; Janssen *et al.* 2010). Janssen *et al.* (2008) also found that a combination of genetic variation in the introns of IFN-γR1/2 receptor and of MAPK6/8 was correlated to AD treatment response (*cfr*. Janssen *et al.* 2010).

The more exhaustive study of Baune *et al.* (2010), with 256 Caucasian patients with MDD(145 women, 111 men) were genotyped for variants rs16944, rs1143643, and rs1143634 in the IL-1β gene (2q14). Response to AD treatment over 6 weeks was defined as remission and response (>50% decrease on Hamilton Rating Scale for Depression–21-question). Therefore, they suggest a negative genetic effect of the IL-1β gene involving the GG genotypes of two SNPs (rs16944, rs1143643) on pharmacological response and amygdala and ACC function that taken together increase the risk of non-remission over 6 weeks of AD treatment in MDD (Baune *et al.* 2009).

The studies in genetics show various polymorphisms in genes related to cytokine production and action that can cause vulnerability to suffer MDD. The "low IL-1β producer" polymorphism was associated with higher depressive symptom severity and less reaction to treatment, compared to the "high IL-1β producer". In essence, all this findings reveal that cytokine function may vary among individuals depending on each individual genotype. Ergo, genetics can make you more or less vulnerable to suffer this disorder or, by contrast, make you more or less responsive to pharmacological treatment.

Up to now, we have seen how the different PICs interact with the CNS, the endocrine system and how they depend on genetics polymorphisms. In the next few pages we will, briefly explain the interactions between the leading treatment for MDD and the IS, and how this interaction influence the efficacy of these treatments regarding the antidepressant-resistant patients.

5. Antidepressant therapy of Major Depressive Disorder

According to Walker (2013) the prescription of SSRIs is a major component in the medical treatment of mood related psychopathology. We will now discuss the influence of AD on cytokines function and its efficacy within the treatment of MDD, i. e. the

impact of AD on cytokines and the influence of cytokines in AD function, regarding the high rates of non-responsive patients with MDD to pharmacological treatment.

5.1. *Antidepressants effects on cytokine function.*

It is now widely accepted that AD have effect on cytokine function (Xia, DePierre, and Nassberger, 1996; Szuster-Ciesielska, Tustanowska-Stachura, Slotwinska, Marmurowska-Michalowska, and Kandefer-Szersze, 2003; Diamond, Kelly and Connor, 2006; Miller *et al.* 2009; Janssen *et al.* 2010; Maes *et al.* 2012; Anders *et al.* 2013). Recently, several studies have analysed the influence of AD on cytokine levels and function, in both *in vitro* and *ex vivo* studies (Janssen *et al.* 2010).

But before we start this part, and in order to understand this interaction, we must go back to the sickness behaviour, a behavioural complex induced by infections and immune trauma mediated by PICs. It is an adaptive response that enhances recovery by conserving energy to combat acute inflammation (Maes *et al.* 2012).

It is postulated that AD may prevent the onset of such sickness behaviour by modulating PICs. Depressed patients, who are otherwise healthy, have increased levels of PICs (IL-1, IL-6, TNF-α, etc.), acute-phase proteins, chemokines, and adhesion molecules (Miller *et al.* 2009; Janssen *et al.* 2010). Pharmacologic interventions that have established antimicrobial, immune-enhancing, or anti-inflammatory properties also merit more study for their potential AD effects. For example, minocycline, a second-generation tetracycline antibiotic, has demonstrated anti-inflammatory and AD effects in both human and animal studies (Pae *et al.* 2008, *cfr.* Anders *et al.* 2013). Or, Xia *et al.* (1996) showed that the AD imipramine, clomipramine, amitriptyline, fluoxetine and citalopram all inhibit transformation of lymphocytes to blastoid forms. The results may indicate that AD affects alterations in human immune cells and, therefore, they may also affect cytokine production by immunocompetent cells.

It should be noted that neither *In vitro* or *Ex vivo* methods simulate true biological processes and while these methods have established themselves as standards in immunological research in neuropsychiatric disorders, some care needs to be taken in extrapolating from these studies to the human condition (Janssen *et al.* 2010).

Xia *et al.* (1996) studied how tricyclic AD (TCAs) influences cytokine release by T lymphocytes and monocytes respectively. They demonstrate that the TCAs imipramine, clomipramine and the SSRI citalopram inhibit cytokine release from human T cells, as well as from monocytes *in vitro*. For example, Citalopram was equality as potent as imipramine and clomipramine in inhibiting IL-6 release after long-term exposure of monocytes to LPS (lipopolysaccharide), and all TCAs elevated intracellular cAMP concentrations significantly in T lymphocytes and monocytes. This inhibition may be related to the mechanism underlying the therapeutic efficiency of these drugs in patients with major depression, a possibility which should be further explored in the future.

Research by Szuster-Ciesielska, et al. (2003), found that AD imipramine and minserine decreased the production of PICs (IL-2, IL-4, INF-γ and IL-12) while they stimulated anti-inflammatory cytokines such as IL-10 and TGF-β.

Following the same stream, and also in an *in vitro* experiment, Diamond *et al.* (2006) examined the effect of first and second generation AD, with selectivity for the serotonin transporter (fluoxetine and clomipramine) or the noradrenaline transporter (reboxetine and desipramine) on monocyte and T-cell derived cytokine production. Their sample was made by 3 male and 5 female; between 22.6 and 2.3 years. Overall, the data generated in this study indicate that IFN-α producing T-cells are the major target of the immunomodulatory actions of AD. Their findings showed that *in vitro* exposure to AD largely fails to alter LPS-induced cytokine production is consistent with a study of Kubera (2004) where a number of AD failed to suppress TNF-α production from diluted whole blood, and is also consistent with an in vivo study Yirmiya *et al.* (2001) in rats where treatment with imipramine and fluoxetine failed to alter LPS-induced IL-1h or TNF-α expression. However their data are at variance with a previous study indicating that AD suppress production of monocyte-derived PICs in human peripheral blood mononuclear cells (PBMC's) (Xia *et al.* 1996; Diamond, *et al.* 2006)

Overall, the *in vitro* studies consistently demonstrate that AD medications produce a strong immunosuppressive effect on whole blood of both depressed patients and healthy volunteers (*cfr*. Xia *et al.* 2006).

In order to name some *ex vivo* study, Lanquillon et al. (2000) found that in patients with an MDD, the treatment response to an AD is related to a differential pattern of immune activation including production of the cytokines IL-6 and TNF-α, IL-6 production was decreased in patients who would later responded to treatment, but was elevated for patients who would prove to be therapy resistant. Production of TNF-α was increased in both groups. After treatment with amitryptyline, cytokine production normalized for all patient groups (Lanquillon, Krieg, Bening-Abu-Shach and Vedder, 2000).

As pointed out in Janssen *et al.* (2010) meta-analysis, in contrast with the findings that depression is associated with higher inflammatory cytokine levels, Rothermundt et al. (2001a) found that cytokine levels of IL-2 and IFN-α were decreased during the acute phase of depression and returned to normal levels after treatment. For the anti-inflammatory cytokine IL-10, a similar pattern was seen, with decreased levels during the acute phase and normalization after treatment. In a later study, Rothermundt et al. (2001b) found no difference of IL-1β production before and after treatment (Janssen *et al.* 2010), and in the same meta-analysis, they quote Anisman *et al.* (1999) study who were not able to detect differences in IL-1β.

These reviewed papers have studied the existing relation and interaction between AD and PICs, showing that for example, fluoxetine and citalopram alter cytokine production. However, the results of these experiments are sometimes contradictory as some have demonstrated the inhibition of PICs and the stimulation of anti-inflammatory cytokines, while some other found that AD failed on suppressing PICs.

5.2. *Antidepressants fail to enhance depressive symptoms.*

Alterations in noradrenergic and serotonergic function in the central nervous system (CNS) have been implicated in the pathophysiology of depression and the mechanism of action of AD drugs (Charney, 1998). Several monoamine-based pharmacological

drug classes have been developed and approved for the treatment of MDD; however, remission rates are low (often less than 60%) and there is a delayed onset before remission of depressive symptoms is achieved (Hillhouse and Porter, 2015). The results of a series of investigations confirm the importance of monoamines in the mediation of depressed mood, but also suggest that other brain neural systems may have more of a primary role than previously thought in the pathophysiology of depression (Charney, 1998). However, in its original form it is clearly inadequate, as it does not provide a complete explanation for the actions of AD, and the pathophysiology of depression it remains unknown. The hypothesis has evolved over the years to include, for example, adaptive changes in receptors to explain why there should be only a gradual clinical response to AD treatment when the increase in availability of monoamines is rapid (Hirschfeld, 2000).

The SSRIs and tricyclic AD (TCAs) are all recognized to alter monoaminergic signalling by blockading 5-HT reuptake, NE reuptake or both (Hyttel, 1993; Owens *et al.* 1997; Shank *et al.* 1988). But despite the widespread prescription of these medications, their use has been a constant subject of controversy and sometimes heated debate (Walker, 2013). While the majority of investigations (*cfr.* Walker, 2013) have supported the efficacy of the SSRIs, several notable studies have suggested that this is not the case, arguing that AD possesses little clinical utility (Kirsch *et al.* 2008; Fournier *et al.* 2010 *cfr.* Walker, 2013).

Evidence suggests that of those receiving adequate medication trials, most will not achieve remission following initial treatment and nearly one-third will not achieve remission even following several treatment steps (Rethorst, Toups, Greer, Nakonezny, Carmody, *et al.* 2012). Remission of symptoms or non-response to treatment typically refers to a situation in which patients fail to respond to standard doses of medication, administered continuously for a minimum duration of six weeks (Fava, and Davidson, 1996 *cfr.* Walker 2013). The non-response rate have been estimated to be between 30 and 50% of patients (Walker, 2013)

The high rates of non-responsive patients to SSRIs has brought controversy regarding its efficacy as main treatment for depression, leading to question whether the monoamine theory provides a complete neurobiological account of depression (Hirschfeld, 2000; Walker, 2013). Of all the other compelling non-monoaminergic and possibly complementary hypothesis of depression, the inflammatory theory is now getting the most attention within literature (Walker, 2013). Research of Dunjic-Kostik *et al.* (2013) seems to be in favour of the notion that a positive correlation between PICs and the treatment efficacy represents a possible trait marker of atypical depression, while IL-6 elevation could be a state marker of acute exacerbation, especially in melancholic depression.

We mentioned before some genetics vulnerabilities which may provoke different types or subtypes of depression, bringing to debate whether depression should or should not be considered as a homogenous condition. Genetic vulnerabilities may also play a role on the responsiveness to treatment in depression, as for example in Yu *et al.* study where a subgroup of MDD patients who were homozygous for the "low producer", -511C allele, were found to have higher depressive symptom severity and less favorable response to fluoxetine treatment when

compared with -511T carriers (*cfr.* Bufalino *et al.* 2013).

Miller *et al.* 2009 found evidence regarding that increased inflammatory activity prior to treatment has reported less response to AD, lithium, or sleep deprivation in depressed patients. Moreover, several studies such as Dowlati *et al.* 2010 reports significantly higher concentrations of PICs (TNF-α and IL-6) in depressed patients with a history of non-response to AD compared with control subjects. In addition, nascents studies suggests that functional allelic variants of the genes for IL-1 and TNF-α, may increase the risk for depression and may be associated with reduced responsiveness to AD therapy (Millet *et al.* 2009). Of note, AD treatment has been associated with decreases in inflammatory markers in 11 of 20 studies according to Miller *et al.* 2009 that examined immune responses as a function of AD therapy.

The study of Lanquillon *et al.* (2000) with a final sample of 24 patients matched with 15 controls during 6 weeks. Their results show that IL-6 levels at admission dichotomized patients into subsequent responders and nonresponders; whereas, the unstimulated secretion of TNF-α was uniformly elevated in both patient subgroups at admission and declined according to the psychopathological improvement. After treatment, IL-6 levels were uniformly normalized, regardless of the clinical outcome. They could state that, in their sample, the production of IL-6 seemed to be a predictive marker for the treatment response; whereas, the changes in TNF-α levels paralleled the clinical course.

The observed inconsistency in research results might be well due to the often disregard confounding factors such as lack of exercise or sleep, smoking habits, use of alcohol, comorbid disorders, medications (Janssen *et al.* 2010; Goldstein *et al.* 2009, *cfr.* Dunjic-Kostic *et al.* 2013) gender or age among many other factors.

By now we have observed how cytokines modulate the onset of this disorder through different pathways and the effectiveness of the pharmacological treatment. Noting that elevated levels of PICs affect antidepressants function and making individuals non-responsive to treatment. Even though evidence show that the monoaminergic hypothesis is not enough to explain the onset of this disorder, the principal pharmacological treatment is based on this hypothesis by belief (and some studies showing) that monoamine-based drugs act as anti-inflammatory in depressed patients, lowering levels of PICs.

Although there is evidence showing that antidepressants may have anti-inflammatory properties, antidepressants fail to enhance depressive symptoms in a large number of depressive individuals. The non-responsiveness of some individuals is belief to be consistency of elevated levels of specifics PICs. In the next few pages we will briefly expose other treatment approaches such as anti-inflammatory drugs or behavioural therapies shown to help the pharmacological treatment lowering PICs or elevating anti-inflammatory cytokines.

6. Other treatment approaches

Converging evidence suggests that depression is often an inflammatory/immune-mediated response to infection, vulnerability to infection, and/or chronic activation of the innate IS. This inflammatory response is stimulated by increased production of PICs, which have wide-ranging effects on both neuroendocrine and neuronal systems, including an

inhibitory influence on serotonergic transmission (Anders *et al.* 2013).

The notion that moods may serve as a behavioural defense against infection, carry important implications for understanding the causes, treatment, and prevention of depression. Some of these implications pose a challenge to conventional wisdom; for example, if symptoms of depression are serving a protective function in the face of immune challenge, then the goal of reducing depressive symptoms to ease emotional distress should be balanced against the need to first identify and treat possible underlying immune factors (Anders *et al.* 2013).

Inflammation, as many authors affirm (*cfr.* Janssen *et al.* 2010) is closely linked with behavioural parameters such as lack of exercise or sleep, alcohol abuse, and smoking, as well as with medical comorbidities including coronary artery disease, obesity and insulin resistance, osteoporosis, and pain (Janssen *et al.* 2010; Rethorst *et al.* 2013). Some of these factors influencing immune vulnerability are commonly addressed in mental health treatment settings and can be alleviated with traditional forms of therapy including cognitive behaviour therapy and mind-body relaxation techniques, as well as pharmacological interventions (Anders *et al.* 2013).

6.1. *Anti-inflammatory pharmacological treatment*

A promising line of research in the search for improved pharmacologic treatments of depression involves anti-inflammatory cytokine antagonists. For example, in animal studies, the use of the IL-1β receptor antagonist IL-1ra prevented the development of depression-like behavioural and neurochemical changes in response to chronic stress exposure (*cfr.* Anders *et al.* 2013).

In a different line of investigation, Warner-Schmidt *et al.* (2011) assessed whether nonsteroidal anti-inflammatory drugs (NSAIDs) could play a role in the treatment outcome of depressed individuals taking SSRIs. They postulated evidence that AD increase brain levels of certain cytokines, which increase p11 levels (a small acidic protein that interacts with specific serotonin receptors to regulate their trafficking and influence their localization at the cell surface), which then induce antidepressant-like behavioural responses (Warner-Schmidt, Vanover, Chen, Marshall and Greengard 2011), and found that human patients reporting concomitant NSAID or other analgesic treatments showed a reduced therapeutic response to citalopram. Finally they suggest that NSAIDs and other analgesics may potentially interfere with the therapeutic efficacy of SSRIs.

And, at the end of their paper "Antidepressant effects of SSRIs are attenuated by anti-inflammatory drugs in mice and humans", they adventure to urge the medical community to consider these findings when designing treatment strategies for their patients that include SSRIs (Warner-Schmidt *et al.* 2011).

In studies of adults with depression, cytokine antagonists have also been found to have antidepressant-like effects. However, conflicting results have been reported for TNF-α antagonists such as infliximab, in that depressed patients with higher levels inflammatory markers especially C-reactive protein (CRP) prior to treatment may benefit from such treatment as opposed to a general benefit in depression (Raison *et al.* 2012 *cfr.* Mills *et al.* 2013). Moreover, anti-inflammatory medications have also

been found to have antidepressant-like effects. For example, acetylsalicylic acid added to fluoxetine led to increased remission rates in depressed patients previously unresponsive to fluoxetine alone (Mendlewicz *et al.* 2006 *cfr.* Mills *et al.* 2013).

Other agents and treatment programs that have anti-inflammatory actions or block actions of cytokines, such as physical exercise and omega-3 polyunsaturated fatty acids (PUFAs), may have a role in the treatment of depression (Mills *et al.* 2013).

6.2. *Behavioural treatment*

Physical exercise is believed to exert similar anti-inflammatory effects improving depressive symptoms, but it is unknown if exercise affects directly inflammation in MDD patients (Rethorst, *et al.* 2012), some other authors claim that the effect of exercise is more globally mediated through various pathways of the neuroIS (Eyre and Baune, 2011 *cfr.* Mills *et al.* 2013). As recently extensively reviewed by these authors, consistent exercise/physical activity has been shown to reduce levels of IL-1β, TNF-α and IL-6, and Kaliman's group research on epigenetic changes related the response to environmental exposures such as diet and physical exercise with reduced levels of cytokines detected in human peripheral tissues (*cfr.* Kaliman, Álvarez-López, Cosín-Tomás, Rosenkranz, Lutz, *et al.* 2014).

On the other hand, a meta-analysis of 10 double-blind, placebo-controlled studies in adult patients with mood disorders receiving omega-3 polyunsaturated fatty acids, indicated an AD effect of omega-3 PUFAs (Lin and Su, 2007 *cfr.* Mills *et al.* 2013). However, the authors noted that it is premature to draw firm conclusions based on the findings due to the heterogeneity of the different study methodologies. Given the implication of omega-3 PUFAs in depression, it is therefore interesting that omega-3 PUFAs have the capacity to decrease the production of PICs, and exert strong anti-inflammatory effects (Maes *et al.* 2009 *cfr.* Mills *et al.* 2013).

Meditation practices may impact physiological pathways that are modulated by stress and relevant to disease (Pace, Negi, Adamec, Cole, Sivilli, *et al.* 2008; Kaliman *et al.* 2014). Mindfulness based interventions, which intentionally cultivate attentional skills, have become an increasingly popular approach and have been associated with improvements in physical health; however, the mechanisms underlying these changes are unclear. However, it may be that the effect of compassion meditation on stress responses is dose dependent and only apparent in individuals who commit to some minimum amount of practice time (Pace *et al.* 2008). Tomfohr *et al.* (2013) explored the relationship between trait mindfulness, blood pressure (BP) and IL-6 (Tomfohr, Pung, Mills, Paul, and Edwards 2013). Their study had 130, young adults [M (SD) age = 21.7(2.7) years] reported trait levels of mindfulness (Five Facet Mindfulness Questionnaire).

Mindfulness meditations involve the development of awareness of present-moment experience with a compassionate, non-judgmental stance (Hölzel *et al.* 2011). Several studies have documented the positive impact of mindfulness-based programs on symptoms of anxiety and depression, as well as improvements in sleep patterns and attention (*cfr.* Hölzel *et al.* 2011). On the epigenetic study of Kaliman *et al.* (2014), they demonstrated that mindfulness-based stress reduction (MBSR) program reduced cytokine secretion, oxidative stress and DNA damage, increased natural killer cell

activity and decreased interleukin secretion in women recently diagnosed with early stage breast cancer, and increased CD4+ T lymphocyte counts in HIV infected subjects.

Given the long-recognized ability of cortisol to suppress innate immune activity, it is intriguing that participants who practiced compassion meditation had reduced IL-6 responses in the absence of clear changes in cortisol reactivity to the Trier social stress test (TSST). Pace *et al.* (2008, 2006) has reliably measured increases in this cytokine in response to the TSST in separate populations and has shown that medically healthy men with depression have increased IL-6 responses to the TSST when compared to men without depression.

7. Discussion

Since the introduction of the macrophage hypothesis of depression in the earliest 1990 by Smith, it has become clear that there is a bidirectional relationship between depression and immune functioning (Janssen *et al.* 2010).

Present pharmacological treatment of depression fails in a higher percentage than, pharmacological industries, health careers or depressed patients would like. Lots of hypothesis has been made, and the one that concerns this paper has been receiving special attention in the last years. The cytokine hypothesis of depression is one of the results of this general effort of health sciences to lower the percentage of non-remission patients and is leading the investigation to the awareness of two concrete interleukins, IL-6 and TNF-α in MDD, especially atypical cases, those who does not respond correctly to any treatment.

In this paper we have briefly reviewed four alternative or complementary treatments to AD, one half is pharmacological, and the other is behavioural proposals of treatment: omega3, nonsteroidal anti-inflammatory drugs, exercise and mindfulness.

Mindfulness-based technique has demonstrated to have significant similar effects than anxiolytics in imaging magnetic resonance therefore meaning that it decreases stress and enhances quality of life. It is currently demonstrated that helps to reduce PICs in MDD patients, so it may be interesting to consider the possibility of mixing both AD therapy with learning and application of mindfulness.

Another important approach to enhance MDD treatment is pharmacogenomics, which focuses primarily on genetics. In this paper we have exposed that depending on the polymorphisms or methylation of some genes, the efficacy of the AD may vary. There is an increasing need of further investigation in this field, with the intention of determining either different biomarkers for AD response, alleles and polymorphisms that affect the predisposition to suffer MDD, the response to AD or PICs levels prior treatment.

Last, we find relevant to mention that there are still some hypothesis about cytokines depression-induced, such as the unbalance of pro and anti-inflammatory cytokines in depressed patients, and the relation between the subtype of depression and cytokine levels. As noted, in various investigations, it has been found a relation between MDD with melancholic features to be more related with higher levels of IL-6, while MDD with atypical features was related with decreased levels of IL-6 and TNF-α (Fumaz, Gonzalez-Garcia, Borras, Ferrer, Munoz-Moreno *et al*. 2009; Dunjnc-Kostic, *et al.* 2012). We believe

these hypotheses should also been taken to consideration inasmuch as they may predict the disorder onset, and treatment inequality in MDD patients.

Although there is now a strong agreement/consensus about the existence of the interaction between the immunological system and the CNS, and therefore with AD, there are still open debates about the real importance of this relationship. Many fronts remain still to investigate and discuss about, but given the relevance of the Major Depressive Disorder in the more developed countries, laboratories, hospitals and universities from all over the world are investigating in the possibilities to either enhance the efficiency of the current AD or to find another way to heal depressed patients

8. Limitations

Our paper main limitation is the heterogeneity of the samples, contradictory results or other uncontrolled factors that may influence on PICs or MDD, such as the diagnostic criteria used for the assessment of depression, across the various studies reviewed. Also, due to the relative youth of this subject, most of these findings are not replied.

Therefore we propose further investigation on this hypothesis and all its variants together with the alternative therapies which may contribute to the enhancement of the treatment efficacy.

9. Conclusions

- The role for dysregulation of the IS in the pathogenesis of MDD is well established. Biological mechanisms involved in the relationship between immune activation and depression could be influenced by underlying genetic vulnerability.
- The first clue about the relation between the IS and the CNS was sickness behaviour which symptoms resemble to depression.
- Until recently the main hypothesis of depression was based on monoamine-neurotransmitters disturbances. However, the lack of efficacy of monoamine-based treatments has put into consideration whether the monoamine theory provides a complete neurobiological account of depression.
- There are numerous studies addressing fundamental pathways by which cytokines may contribute to depression such as monoamine pathways (5-HT, DA or Glu), neuroendocrine system (HPA axis), growth factors (BDNF) and genetics.
- Increased levels of PICs have been found repeatedly in depressed individuals, prompting the formulation of the "cytokine hypothesis of depression". However, several studies did not found any association between cytokines levels and symptoms of depression.
- Studies have analysed these influences finding that AD affects human immune cells then they also may affect cytokine production. Tricyclic and SSRIs, both demonstrate inhibition of cytokine release and production of other PICs. *Ex vivo* studies observed that treatment response to AD was related to the pattern of immune activation.
- Other factors non-widely taken into consideration in treatment response are lack of exercise, smoking, medications or even gender and age, may play an important role on treatment-response rates.
- Lots of nascent pathways have been hypothesized in order to ameliorate the symptoms and help AD accomplish its purpose. An anti-

inflammatory cytokine antagonist has been taken into consideration; however conflicting results have been reposted.
- Other agents considered to have anti-inflammatory actions are exercise and Omega-3 fatty acids, but it remains unknown the mechanism by which these may act in order to decrease pro-inflammatory cytokines levels.
- Meditation practices also seem to impact physiological pathways that are modulated by stress and relevant to MDD, such as mindfulness-based interventions.

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FE D'ERRADES

Després de l'entrega del treball de fi de grau, i en posteriors revisions, les autores del treball "*Treatment failure in major depression associated with chronic inflammation of the immune system: a psychoneuroimmunological hypothesis"* declaren que han trobat errors en els seguents apartats:

A totes les pàgines: el número a peu de pàgina està en una font diferent.

Pàgina 1, es localitza l'estudia *Barcelona* i és realitzat a *Bellaterra.*

Pàgina 14, paràgraf que comença amb "*The SSRIs, tricyclic AD (TCAs) ~~and SNRIs~~ are all recognized to alter monoaminergic signalling by blockading 5-HT reuptake, NE reuptake or both […]"* hauria de ser *"The SSRIs and tricyclic AD (TCAs) are all recognized to alter monoaminergic signalling by blockading 5-HT reuptake, NE reuptake or both".*

Pàgina 14, paràgrag que comença amb *"The high rates of non-responsive patients to SSRIs has brought controversy regarding its efficacy as main treatment for depression […]"* hi falta una paraula al final, i hauria de quedar: *"The high rates of non-responsive patients to SSRIs has brought controversy regarding its efficacy as main treatment for depression, leading to question whether the monoamine theory provides a complete neurobiological account of depression (Hirschfeld, 2000; Walker, 2013). Of all the other compelling non-monoaminergic and possibly complementary hypothesis of depression, the inflammatory theory is now getting the most attention within literature (Walker, 2013). Research of Dunjic-Kostik et al. (2013) seems to be in favour of the notion that a positive correlation between PICs and the treatment efficacy represents a possible trait marker of atypical depression, while IL-6 elevation could be a state marker of acute exacerbation, especially in melancholic* ***depression****".*

Pàgina 18, paràgraf que comença amb *"Mindfulness ~~is a relaxation technique which~~ has demonstrated to have significant similar effects than anxiolytics in imaging magnetic resonance therefore meaning that it decreases stress and enhances quality of life […]"* i haría de ser *"Mindfulness-based technique has demonstrated to have significant similar effects than anxiolytics in imaging magnetic resonance therefore meaning that it decreases stress and enhances quality of life".*

Ens disculpem per les possibles molèsties que aquests errors hagin pogut ocasionar al lector.

Andrés Rodríguez, Laura

Báez Sesto, Paula María

Executive summary

Treatment failure in major depression associated with chronic inflammation of the immune system: a psychoneuroimmunological hypothesis

Andrés Rodríguez, Laura and Báez Sesto, Paula María

Universitat Autònoma de Barcelona

Bellaterra, Catalunya, 2015

1708 words

Key stakeholders

The stakeholders for our paper may be the medical community more concretely; healthcare professionals prescribing antidepressant medication and healthcare professionals investigating on alternative therapies to decrease the treatment failure should be main recipients of the present document, alongside with researchers on the antidepressant medication field, patients suffering treatment-resistant depression and its families.

In the last decades, the antidepressant treatment has been a contentious field of research in which the leading monoamine based treatment of depression has been letting the 30% to 50% of patients with acute phase of major depression without improvement. Therefore researchers are constantly searching for the remedy to this blemish in the treatment of depression promoting the conception of the cytokine hypothesis of depression which defends the idea that cytokines interact not only with the central nervous system (CNS), but also with the antidepressant treatment. To the best of our knowledge, there is not any study evaluating the efficacy of a dual therapy that may include both, the current antidepressants (AD) therapy and one that helps to reduce the chronic inflammation of the CNS. This is the reason why we encourage research stakeholders to investigate the effectiveness and also the possible differences between pharmacological and behavioural treatments efficacy for the chronic inflammation of the immune system (IS).

Thus healthcare professional stakeholders should consider, previous to the selected drug therapy, a blood analysis in order to assess whether the patient has a chronic inflammation of the CNS, and if so, apply dual therapy including both, the current AD therapy and one that helps to reduce the chronic inflammation of the CNS. But since an analysis of pro-inflammatory cytokines is very expensive, it would be equally effective a generic and simple indicator of inflammation which results to be an inexpensive high-sensitivity C-reactive protein (hsCRP) which costs less than 5 €.

INTRODUCTION

Psychoneuroimmunology investigates roughly the interaction between the IS and the CNS. A relevant body of research has been focusing on both the causes and the remedies of **major depressive disorder** (MDD) which is predicted to be the second leading cause of disability by 2020.

Depressive syndromes and MDD are exceedingly common, they are a chronic and recurrent disorder with residual disability, and yet the contributing factors to its nature are not entirely understood. The acknowledgment of **sickness behaviour** was a seed to the cytokine hypothesis of depression, which defends that increased levels of pro-inflammatory cytokines (PICs) are present in MDD patients. It is now generally accepted that immune dysregulation plays an important role in the pathogenesis of MDD. There are good evidences suggesting that inflammation can contribute to the development of depression but it is less evident that blocking inflammation will lead to a reduction of depressive symptoms or be efficacious in treatment-resistant depression.

We aim to clarify how some specific molecules of the immune system (cytokines) interact with AD, and how this interaction affects the efficacy of the pharmacological treatment in MDD. We also attempt to analyse an alternative depression treatment which is based on the hypothesis that improving the inflammatory state of the immune system alleviates the depression symptoms.

METHODOLOGY

This review encompasses the literature mainly published between 2004 and 2015. The limited review to these years obeys the intention to best characterize current thinking about the relationship between immune activation and depression. We built a systematic review of the pubmed and psychinfo among other databases. We have also searched in the firsts reviewed articles' bibliography in order to select those we found more interesting. With an exception for those articles that are the base of knowledge in psychoneuroimmunology and those related with depression. The searches applied in the databases were Psychoneuroimmunology AND depression AND treatment failure, and also, Psychoneuroimmunology AND depression AND cytokines AND antidepressants. We have finally used 42 reviews or meta-analysis, all of them in English.

RESULTS

Aetiology hypotheses of Major Depressive Disorder

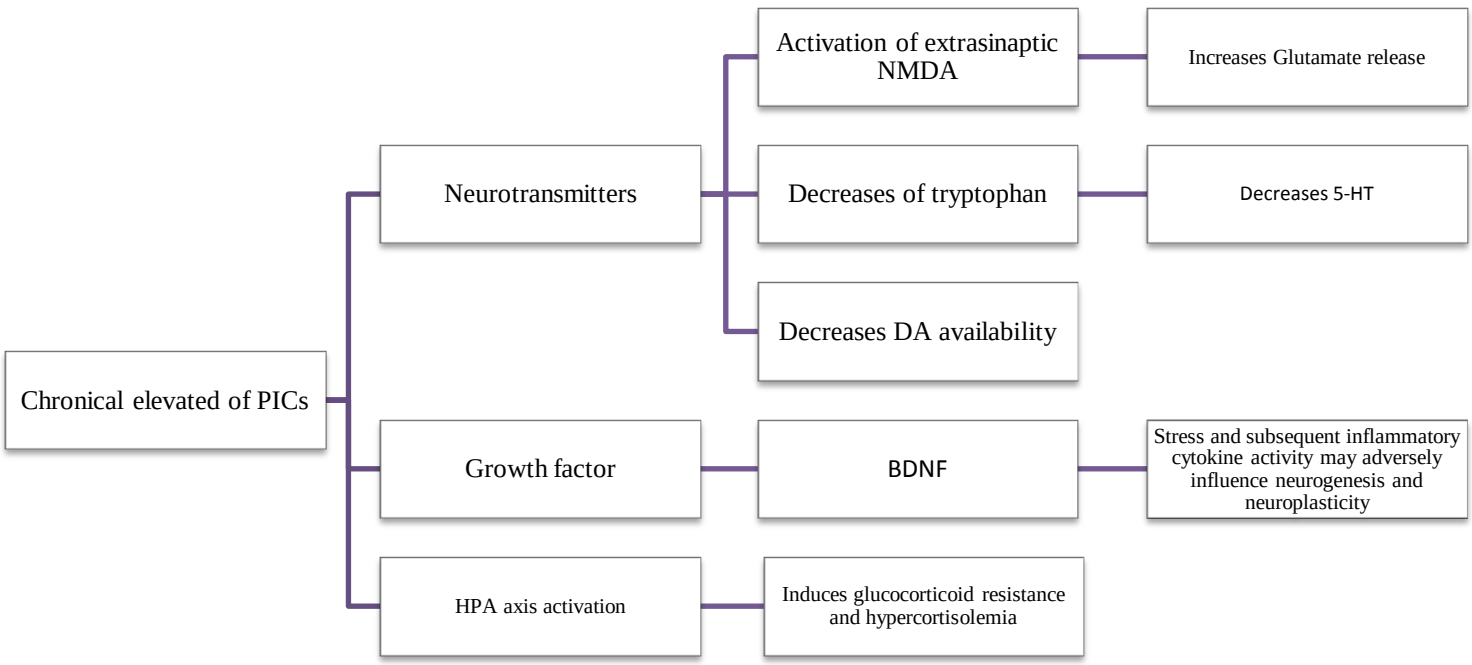
The leading hypothesis of depression defends that depression is caused by a deficiency in synaptic concentrations of monoaminergic neurotransmitters including serotonin and norepinephrine which has been called the **monoamine hypothesis of depression** and has become the basis for most of the treatments in the market. However, the efficacy of antidepressant drugs based on the fundamental premise of the monoamine hypothesis has been limited, with estimates between 30% and 50% of individuals treated with antidepressant medication do not show adequate response. The credibility of the monoamine theory and the therapeutic efficacy of these compounds in the treatment of depression have been extensively criticized. Research on the immune system and its role in the etiology of depression has emerged as an especially promising area for study, in particular, the role of immune-activated inflammatory cytokines, a key area of focus in understanding the neurobiological pathways that trigger depressive states by way of direct and indirect effects on hypothalamic-pituitary-adrenal (HPA) axis, and by altering monoamine neurotransmitters in multiple regions of the brain.

The insufficiency of the monoamine hypothesis to explain several aspects of mood regulation has resulted in an extended research for new neurobiological basis of depression. Increased levels of PICs have been repeatedly observed in depressed individuals prompting the formulation of the "**Cytokine hypothesis of depression**". Cytokines are the key mediator of inflammation; therefore they can alter neurochemical and neuroendocrine processes that have wide-ranging effects on physiology and behaviour. In this review, we focus primarily on PICs interleukine-1 (IL-1), IL-6, and Tumour Necrosis Factor-α (TNF-α), which together coordinate a variety of cell functions that stimulate and enhance inflammation. The most obvious possibility is that cytokines travel to the brain in the bloodstream and cross the blood-brain barrier. There are specific receptors for IL-1, IL-6 and TNF in the brain and neurons. Also blocking IL-1 receptors in the brain can prevent some of the sickness like responses to peripheral administration of cytokines.

> ***Cytokines*** *are secreted proteins by immune cells and act on other cells to coordinate appropriate immune responses. Cytokines include a diverse assortment of interleukins, interferons, and growth factors.*

However, as cytokines are large lyophobic molecules they are not likely to cross the blood-brain barrier and enter the brain. Numerous investigations proposed different mechanisms such as, active transport, weak brain-barrier areas, and the existence of receptors inside the blood vessels that may allow cytokines access to the brain; however it does not seem to be sufficient to produce psychological changes. There are other alternative communication pathways between the brain and the immune system. The CNS receives neural and humoral signals about the peripheral inflammatory response thought PIC-induced activation of afferent vagal signals at the sensory nuclei of the solitary tract.

The specific effects of PICs on depressive-related pathways are virtually every pathophysiologic domain relevant to depression, including neurotransmitters metabolism, endocrine system activation and growth factors modulation:



NMDA (N-methyl-D-aspartate receptor); BDNF (Brain-Derived Neurotrophic Factor); HPA axis (Hypothalamic-Pituitary-Adrenal axis)

Regarding **genetics**, twin studies have shown that phenotypes depression and increased immune activation are heritable, and that the link between immune activation and depression, at least in part, is due to shared genes regulating immune function and inflammatory response. Interactions between immune-cells, monoamine, endocrine system, and neuropeptides seem to be variously related with several functional gene polymorphisms associated with vulnerability to depression or with certain symptom dimensions of this cytokine-induced depression. This is why we also may encourage a genetic research on this psychoneuroimmunologycal field.

Treatment resistance in major depression disorder

The selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) are recognized to alter monoaminergic signalling by blockading 5-HT reuptake, NE reuptake or both; however several notable studies have reported a lack of efficacy, arguing that antidepressants possess little clinical utility.

A positive correlation between PICs and the treatment efficacy represents a possible trait marker of atypical depression, while IL-6 elevation could be a state marker of acute exacerbation, especially in melancholic patients. The prior to treatment increase of inflammatory activity has reported less response to antidepressants, lithium, or sleep deprivation in depressed patients. Moreover, several studies report significantly higher concentrations of PICs (IL-6 and TNF-α) in depressed patients with a history of non-response to antidepressants compared with control subjects.

> ***Remission*** *of symptoms or non-response to treatment typically refers to a situation in which patients fail to respond to standard doses of medication, administered continuously for a minimum duration of six weeks*

Alternative proposals:

Converging evidence suggests that depression is often an inflammatory/immune-mediated response to infection, vulnerability to infection, and/or chronic activation of the innate immune system. In our extensive research we found a complementary drug therapy and three complementary behavioural therapies.

The **complementary drug therapy** comes from a promising line of research in the search for improved pharmacologic treatments of depression involving anti-inflammatory cytokine antagonists. For example, the use of the IL-1β receptor

antagonist IL-1ra, in animals, prevented the development of depression-like behavioural and neurochemical changes in response to chronic stress exposure.

The **complementary behavioural therapies** are three: 1) physical exercise is believed to exert similar anti-inflammatory effects improving depressive symptoms, but it is unknown if exercise affects directly inflammation in MDD patients. 2) Relaxation techniques, such as Jaboson's. 3) Meditation which may impact physiological pathways those which are modulated by stress and relevant to disease. Although several studies have documented the positive impact of mindfulness-based programs on symptoms of anxiety and depression, as well as improvements in sleep patterns and attention, we urge health community to investigate the mechanisms underlying these changes which remains unclear.

IMPLICATION FOR RESEARCHERS

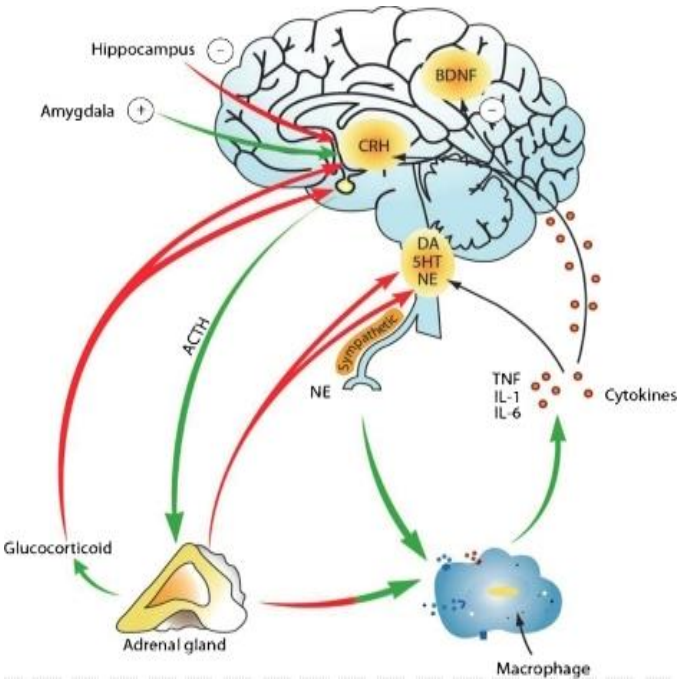
Further investigation should be carried in two main streams; the first may seek to understand all the causes of the failure in AD treatment; and the second and most important should be the investigation in the efficacy of the proposed dual therapy that may include both, the current AD therapy and one that helps to reduce the chronic inflammation of the CNS. We urge research stakeholders to execute further and deeper investigation on this field, to evaluate the effectiveness of the dual treatment. Lines of investigation may be whether the AD are necessary or not with the application of these techniques and also to determine the % of depressed people whom may benefice of these innovation in treatment.

Research: *Treatment failure in major depression associated with chronic inflammation of the immune system: a psychoneuroimmunologycal hypothesis*

Andrés Rodríguez, Laura and Báez Sesto, Paula María

Universitat Autònoma de Barcelona: Bellaterra, Catalunya, 2015

Pharmacological treatment is, at present, the first option for battling depressive symptoms despite the documented lack of efficacy of antidepressants therapy based in the hypothesis that depression might be caused by a **dysregulation of monoamine levels**, such as serotonin or norepinephrine, in the brain. The present review submitted by Paula Báez and Laura Andrés from the *Universitat Autònoma de Barcelona* aims to clarify reasons why antidepressants treatment fails in 30 to 50% of depressed patients, above all, those suffering **Major Depressive Disorder** which is expected to be the second cause of disability by 2020. Several investigations gathered by the authors show a significant interest in agents from the **immune system** known as ***cytokines***, especially pro-inflammatory cytokines. These molecules seem to be implicated in both onset and treatment response in depressed individuals.



Pro-inflammatory cytokines are responsible for the inflammatory response facing infection and causing behavioural changes known as ***sickness behaviour***, which are similar to depressive symptoms, such as diminished sleep and activity, among others. Now that the role of pro-inflammatory cytokines in depression are not doubted, it has been extensively demonstrated that a high percentage of **unresponsive depressive patients have elevated levels of these molecules** impacting on the efficacy of antidepressants. Anyway the authors encourage further investigation on this subject.

Since the lack of efficacy of monoamine-based pharmacological treatment (in some of the individual suffering depression) and the role of pro-inflammatory cytokines are demonstrated facts, some investigators bring forward **new treatment proposals**. All of them founded by the belief that **alleviating chronic inflammation** of the immune system and reducing pro-inflammatory cytokines levels will somehow **enhance depressed symptoms.** The **alternative therapies** proposed by the researchers are "dual therapies" in which classic pharmacological treatment is combined with techniques demonstrated to reduce pro-inflammatory cytokine levels, such as anti-inflammatory cytokines antagonists and meditation.

The authors of this review focus, especially, on **Mindfulness-based** programs which have been highly demonstrated to reduce symptoms of **anxiety and depression**, and have been also associated with **improvements in physical health** although the pathways underlying these changes are unclear. Mindfulness-based stress reduction (MBSR) programs evidence reduction of cytokine secretion, oxidative stress and DNA damage, increased natural killer cell activity and decreased interleukin secretion, among other benefits in depressed patients.

Even though the results of this investigation are inconclusive the authors propound further investigation on this subject, in order to clarify the role of cytokines in treatment response and dig deeper into new therapy proposals to bring the spotlight to treatment-resistant depressive patients.