Inflammation and depression but where does the inflammation come from?

Angelos Halaris

Purpose of review
Up until the latter part of the previous century, the monoamine theory guided our understanding of psychiatric disorders, notably depressive illness in its various phenotypic manifestations. The purpose of this review is to provide an overview of newer theories that allow a deeper understanding of brain dysfunction and neuropsychiatric disease entities such as depressive illness. One such key theory is the theory of inflammation as a result of stress-induced immune system activation.

Recent findings
Stress activates the hypothalamic–pituitary–adrenal axis and the sympathetic branch of the autonomic nervous system [sympathetic branch (SNS)] with a concomitant reduction in vagal tone. This homeostatic imbalance makes a simultaneous dual contribution to the resulting proinflammatory state of depression. SNS stimulation results in upregulation of proinflammatory signaling, whereas diminution in parasympathetic tone affects the body's immune response. The resulting proinflammatory status has been closely associated with multiple organ dysfunction and comorbid conditions.

Summary
The advent of innovative theories about the pathophysiology of psychiatric disorders has ushered in a new era on the basis of the role of the immune system and inflammation in mediating depression in its multifaceted manifestations. Extensive studies have confirmed the proinflammatory status in depression and causal relationships with neurotransmitter dysregulation. Equally importantly the role the autonomic nervous system plays in this complex and multifactorial interplay of body systems is being increasingly elucidated.

Keywords
autonomic nervous system, depression, inflammation, neuroprogression, stress

INTRODUCTION

The term 'depression' is a term commonly used worldwide to refer to a serious illness with many subtypes. I prefer to use the term depressive illness to subsume the most common forms, notably major depressive disorder (MDD) and depression associated with bipolar disorder (BDD). Other designations include atypical depression, dysthymic disorder, and variants denoting the course of depressive illness, namely chronic, recurrent, relapsing, and residual. Psychotic features can be present. No matter what the subtype or designation of depressive illness, it is a serious medical illness. It comprises a multitude of cognitive, affective, and physical symptoms and is in most cases characterized by recurrences and a chronic course. It is associated with higher rates of chronic physical disease, increased healthcare utilization, and impaired functioning. There is significant morbidity, mortality, disability, and economic burden worldwide [1,2]. In addition to the psychosocial and psychophysical dysfunctions associated with depressive illness, several conditions show rather high comorbidity, notably, cardiovascular and cerebrovascular disease, type-2 diabetes, autoimmune diseases, neurodegenerative disorders, cancer, obesity, and intestinal conditions [3–7]. Suicidality is common and can have a lethal outcome that may not be preventable. Even in industrialized countries rates of access to treatment remain low, the treatment received is often inadequate, and response rates are unacceptably low. For MDD and BDD, only an average of one-third of

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Curr Opin Psychiatry 2019, 32:422–428
DOI:10.1097/YCO.0000000000000531

KEY POINTS

- Depressive disorder is a serious medical illness comprising cognitive, affective, and physical symptoms and is characterized by recurrences and a chronic course. It is associated with higher rates of chronic physical disease, increased healthcare utilization, and impaired functioning.
- Stress plays a critical role in depression ultimately leading to pervasive mental status changes, *chronic low-grade inflammatory reaction* and pathological alterations to the function and structure of many organ systems.
- Stress-induced activation of the immune response alters neurotransmission leading to neurotransmitter imbalances, such as serotonergic deficiency, and increased production of neurotoxic substances contributing to disease progression. Immune system activation is reflected in abnormal levels of inflammatory mediators known as cytokines in serum, plasma, and cerebrospinal fluid.
- The concept of neuroprogression subsumes the progressive, recurrent, and relapsing course of a specific disorder. Likely pathophysiological substrates that contribute to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, and loss of synaptic plasticity.

patients will achieve symptom remission, whereas a full one-third fail to respond at all even after multiple antidepressant drug trials.

Epidemiology of depressive illness

Approximately 120 million people worldwide are afflicted with depressive illness of one type or another and it is the leading cause of disability worldwide [8]. Depending on the study, the lifetime prevalence of depressive illness can be as high as 16%, whereas the 12-month prevalence ranges from 3% in Japan to over 9% in the United States [9,10]. Using the disability-adjusted life-years, MDD was classed in 1990 as the fourth leading burden of disease worldwide for both sexes; by 2004, it advanced to third place. The incidence of depressive illness has been steadily increasing over the past decades. According to the World Health Organization's estimate, depressive illness will rank second to heart disease by the year 2020 [11] and will be the leading cause of disease burden by 2030 [10].

The National Health and Nutrition Examination Survey, 2009–2012 [12] has demonstrated that about 7.6% of Americans aged 12 and over had depression (defined as having moderate or severe depressive symptoms in the past 2 weeks). Depression was more prevalent among females and among adults aged 40–59 years. Persons with mild depressive symptoms, as well as those with moderate or severe depressive symptoms, reported difficulties with work, home, and social activities related to their symptoms. Numerous studies have also shown that persons with depression have more functional limitations than those without depression.

DEPRESSION AND INFLAMMATION

Role of stress in depression and inflammation

The significant contribution of stress, real or perceived, and individual stress vulnerability has been known for a long time to contribute to the cause of depression. Mental stress is subject to high individual variability and resilience and varies in intensity and duration. There is a strong genetic component and epigenetic modifications, especially those resulting from early life adversity, can profoundly modify stress susceptibility and stress resilience. Chronic and especially inescapable stress, such as stress associated with chronic illness – physical or mental – low socioeconomic status, dysfunctional relationships, caregiver status, ultimately leads to pervasive mental status changes, *chronic low-grade inflammatory reaction* and pathological alterations to the function and structure of many organ systems.

Stress activates the hypothalamic–pituitary–adrenal axis (HPA) and the sympathetic branch (SNS) of the autonomic nervous system (ANS) with a concomitant reduction in vagal tone. This homeostatic imbalance makes a simultaneous dual contribution to the resulting proinflammatory state of depression. SNS stimulation triggers release of catecholamine in the locus coeruleus and adrenal medulla, resulting in an upregulation of proinflammatory signaling. Stress-induced SNS activation induces proinflammatory responses [13], whereas norepinephrine modulates proinflammatory cytokine transcription via β-adrenergic receptor stimulation [14]. At the same time, diminution in parasympathetic tone affects the body's immune response. This effect occurs, at least in part, through the cholinergic antiinflammatory pathway, as described by Tracey [15]. The imbalance in ANS function, especially if prolonged, as is invariably the case with psychiatric disorders, has profound effects on the immune system. These pathophysiological changes contribute significantly to the comorbidity between psychiatric disorders, notably depression, and other organ systems. Thus, to quote Thayer and Lane [16], autonomic imbalance and

decreased parasympathetic activity, in particular, may be the final common pathway to numerous diseases and conditions associated with increased morbidity and mortality.

Neuroinflammation

Involvement of the immune system in major mental illnesses was first postulated in the early 20th century. A century later, it is now accepted that the immune system and inflammatory processes contribute to brain-related diseases in most, if not all, neurological and psychiatric disorders. Stress-induced activation of the immune response alters neurotransmission leading to neurotransmitter imbalances, such as serotonergic deficiency, and increased production of neurotoxic substances contributing to disease progression. Immune system activation is reflected in abnormal levels of inflammatory mediators known as cytokines in serum, plasma, and cerebrospinal fluid of many patients with psychiatric and neuropsychiatric disorders. A sustained proinflammatory state is believed to be involved in the pathogenesis and pathophysiology of major mental illnesses. Proinflammatory cytokines are produced by activated cells of the immune system, such as activated endothelial cells, monocytes, monocyte-derived dendritic cells, macrophages, T cells, and microglia. The realization that immune cells can be involved in mental illnesses has led to the macrophage–T-cell theory of depression and schizophrenia which was proposed in 1992 and adapted in 1995 [17,18]. Indeed, receptors for inflammatory cytokines are present in various brain nuclei [19], which upon triggering dysregulate important neurotransmitters and neurodevelopmental systems, facilitating the development of psychiatric signs and symptoms.

Inflammation and depression

For decades, the monoamine theory of depression has dominated the field and has been instrumental in enabling the development of innovative therapeutic agents that have been effective in spite of the time lag in producing response, fairly low rates of response and remission, and numerous side-effects [20–22]. More recently, multiple hypotheses have been formulated in an effort to unravel the elusive pathophysiology of depressive illness, including the neurotrophic hypothesis, the cytokine (or macrophage) hypothesis, the glutamate hypothesis, the polyamine hypothesis, and the microbiota–inflammasome hypothesis [23–27,28▪]. However, no single hypothesis can satisfactorily explain the etiopathology, onset, progression, and remission of the disease. This is a reflection of the complexity of the disorder and the multitude of interfacing mechanisms that ultimately lead to the phenomenological manifestations of the disorder. Newer therapeutic strategies involve drugs acting on neuroplasticity-related pathways, gut microbiome modulation, and deep brain stimulation [29▪,30▪,31]. Nevertheless, the quest for a better understanding of the molecular underpinnings of this disease represents an essential step in the identification of efficacious therapeutic strategies that could target the causal biological mechanisms of depressive illness. This is where the inflammation hypothesis of depression holds significant promise as will be discussed below.

The cytokine theory of depression was originally formulated by Smith [32] as 'The Macrophage Theory of Depression' and later expanded by Ur *et al.* [33]. The theory postulated that psychological stress, in conjunction with genetic factors, increases cytokine production and leads to depressive symptoms when specific neurobiological systems are affected, such as the HPA axis and serotonergic transmission. A chronic proinflammatory status reflected in elevated circulating levels of proinflammatory cytokines may thus be central to the pathophysiology not only of MDD and BDD but also likely atypical depression and posttraumatic stress disorder.

The proinflammatory status associated with MDD has been described in the literature dating back to the last decade of the previous century and the reader is referred to excellent reviews on the subject [34,35]. Peripheral measures of pro and antiinflammatory cytokines, commonly referred to as 'inflammation biomarkers' demonstrate variable increases of proinflammatory cytokines, such as IL-2, IL-6, soluble IL-6 receptor, tumor necrosis factor α and IFN-γ, and decreases in antiinflammatory cytokines, such as IL-4 and IL-10. Stimulation of cytokine release or injections of proinflammatory cytokines can induce a syndrome known as 'sickness behavior' that simulates many of the classical symptoms of depression [36]. But although numerous previous reports have shown that proinflammatory cytokines are endogenously overexpressed in depression and other stress-induced disorders, not all depressed patients show such abnormalities [37]. For a more detailed discussion, the reader is referred to critical reviews on this issue [34,13,38▪▪,39]. It should be stated that the degree of cytokine elevations in depressive illness are moderate in comparison to those during physical injury and/or infection. However, by being chronically overexpressed in depressive illness, especially over prolonged periods of time and in patients who fail to respond to antidepressant interventions, cytokines can have

long-term adverse consequences on organ systems, notably the cardiovascular system. Additionally, the sustained immunological imbalance triggers multifaceted dysfunctions, including metabolism, neurotransmission, gut microbiome, and impaired neurogenesis and neuroplasticity [40–42]. Indeed, the neurotrophic hypothesis of depression suggests that depressive illness patients have inflammation-driven decreased neurogenesis, which leads to atrophy of brain areas such as the hippocampus and the prefrontal cortex [43–46]. Not surprisingly, proinflammatory cytokines and increased glucocorticoid production downregulate neurotrophins (such as brain-derived neurotrophic factor and nerve-growth factor) and neurogenesis during and following stress, whereas antidepressant treatment may reverse such decreases [47,48].

In considering the role of inflammation in depression, two questions arise: does a sustained proinflammatory status hinder the effectiveness of antidepressant drug treatments, and does antidepressant therapy normalize elevated levels of proinflammatory mediators. It has been suspected that the chronic proinflammatory status found in depression may delay, diminish, and even thwart antidepressant response. It has therefore been hypothesized that controlling inflammation without inducing immunosuppression might improve antidepressant treatment outcomes. An increasing number of studies point to the benefit of combining an antiinflammatory compound, such as the cyclooxygenase-2 (COX-2) inhibitor, celecoxib, with a standard antidepressant drug [49,50,51]. We have obtained strong evidence that such combination treatment is effective in reversing treatment-resistant bipolar depression and augmenting response [52,53▪,54▪].

With respect to the second question, although the majority of published reports indicate normalization of proinflammatory cytokines with treatment, not all reports agree. Differences in study design, mainly the length of treatment and the type of antidepressant agent utilized, appear to be crucial variables that must be controlled in future studies. Additionally, the time course of cytokine normalization may not precisely coincide with the time frame of clinical antidepressant response. Clarification of the temporal associations between mood improvement and cytokine normalization should be an important aspect of future studies [55].

BRAIN IMMUNE INTERACTION

The central nervous system (CNS) has its own immune system based in microglia and astrocytes and it can operate independently from the peripheral immune system. However, there is communication and cooperation between the two systems. The CNS is involved in regulating immunity, and immune responses in the periphery affect CNS immune responses ultimately triggering behavioral changes. Brain–immune interaction does occur and is exemplified by the link between mood dysregulation, notably depression, and serotonergic transmission [56,57]. It is also accepted that the relationship between the immune system and CNS in general and neurotransmission, in particular, is bidirectional. In response to stress, the release of proinflammatory cytokines is increased. These inflammatory mediators exert a powerful influence on the HPA axis and neurotransmitters critical to mood regulation and cognitive function. Serotonergic transmission in particular, but not to the exclusion of other neurotransmitters, has emerged as a possible 'common denominator' between depressive illness and the immune system. Other neurotransmitters, notably acetylcholine, norepinephrine, dopamine, and glutamate are also implicated but space limitations preclude their discussion. Under inflammatory conditions, infections or oxidative stress, the first rate-limiting enzymatic step in the kynurenine pathway of tryptophan metabolism, the enzyme indoleamine 2,3-dioxygenase (IDO), is activated. The IDO enzymatic activity is enhanced by proinflammatory and inhibited by antiinflammatory cytokines. Overstimulation of IDO leads to tryptophan diversion resulting in serotonin deficiency in the brain [58]. In a parallel enzymatic process, a related enzyme, tryptophan dioxygenase, is activated by cortisol thereby contributing to serotonergic deficiency and production of neurotoxic metabolites in the kynurenine pathway, notably quinolinic acid.

THE CONCEPT OF NEUROPROGRESSION

Neuroprogression subsumes the progressive, recurrent and relapsing course of a specific disorder [59,60]. In some disease entities, it is possible to 'stage' the course of the disorder on the basis of clinical manifestations, and, to the extent that morphological, biochemical, neurochemical, immunological, physiological, and genetic aspects have been established, such parameters as well. An excellent example to illustrate the utility of this concept is cancer diagnosis and treatment. In a similar vein, parameters can be standardized and used to stage neuropsychiatric disease entities although more research to validate promising parameters must still be undertaken. Likely pathophysiological substrates that contribute to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity,

and loss of synaptic plasticity [61]. Neuronal loss and structural changes in the hippocampus, amygdala, orbitofrontal cortex, anterior cingulate cortex, basal ganglia, and pituitary gland have already been associated with progressive disease in certain psychiatric disorders [62,63]. There is also a complex interplay with the monoaminergic, cholinergic, glutamatergic, and GABAergic neurotransmitter systems that require further elucidation. Glutamatergic transmission has recently received attention thanks to the elegant MR spectroscopy studies published by Haroon *et al.* [64,65]. The significant clinical implications of neuroprogression in psychiatric disorders, as well as the biological mechanisms underlying neuroprogression, are the subject of a recently published monograph [66▪▪,67].

CONCLUSION

Depressive disorder is a serious medical illness afflicting significant portions of the population worldwide. It is a highly complex disorder with diversity of phenotypic presentations and extensive comorbidities with other psychiatric and medical disorders. It is associated with higher rates of chronic physical disease, increased healthcare utilization, and impaired functioning. It poses major therapeutic challenges to the clinician due in part to the low rates of response and remission, a chronic and relapsing course, the need for combined therapies and in some instances loss of response with prolonged treatment. Over many decades, intense efforts to unravel the puzzle of the etiopathology of depressive illness have been met only with partial success but significant progress has been accomplished. Our understanding of the underlying mechanisms of depressive illness has gone beyond the monoaminergic theory. The role stress plays in at least triggering a depressive episode and even fueling relapses and chronicity is beyond dispute. Real and perceived stress coupled with individual genetically determined susceptibility disturbs the homeostatic balance of the autonomic nervous system thereby leading to sympathetic overactivity with concomitant diminution in parasympathetic tone. This imbalance, especially if it is prolonged, as is the case with most any chronic illness, initiates a series of downstream events at the center of which is activation of the immune response. A cascade of events ensues resulting in a *chronic low-grade inflammatory reaction*. Such a state in turn through the now established crosstalk between the central and peripheral nervous systems and the immune system induces neurotransmitter imbalances most of which had already been identified with research efforts undertaken during previous decades. One major example here is diversion of tryptophan toward the kynurenine pathway with resulting increase in neurotoxic metabolites. Other systems are also affected, notably the catecholaminergic and glutamatergic systems in conjunction with inflammation. The elucidation of these highly complex and interactive pathways, however, presents enormous opportunities for the development of innovative drug therapies. Lastly, the concept of neuroprogression is being applied to psychiatric illnesses patterned after successful application of the concept in cancer. Neuroprogression subsumes the progressive, recurrent, and relapsing course of a specific disorder. Likely pathophysiological substrates that contribute to neuroprogression in psychiatric disorders in general, and more specifically in depressive illness, include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity, and loss of synaptic plasticity.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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