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SM Journal of Clinical Medicine

Review Article

A Chronic State of Systemic Stress: The Link between Depression and Cardiovascular Disease?

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Article Information

Received date: May 04, 2017
Accepted date: Jun 22, 2017
Published date: Jun 27, 2017

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Keywords Depression; Chronic stress; Cardiovascular disease; Neurobiology; Chronic inflammation; Insulin resistance

Abstract

Depression is one of the most frequent mental disorders in clinical practice, which has been closely associated with impaired daily functioning and quality of life, and increased morbidity and mortality. Although depression has been related to a wide spectrum of medical conditions, the link with Cardiovascular Disease (CVD) appears to be particularly robust in regards to epidemiology and pathophysiology. Indeed, depression and CVD may share a common mechanistic continuum via the molecular phenomena featured in a chronic stress response. In this regard, chronic inflammation, insulin resistance and dysregulation of thrombogenesis may be instrumental in the neurobiological "slippery slope" from chronic stress to depression, and further, to cardiometabolic disease. This article summarizes current knowledge on the pathophysiologic relationship between chronic systemic stress, depression and CVD, highlighting potential novel therapeutic targets.

Introduction

Depression is a very frequent and recurrent mental disorder, which has been linked to diminished daily functioning and quality of life, and increased morbidity and mortality [1]. Depression is currently estimated to affect approximately 350 million people worldwide, and is considered the leading cause of disability globally [2], associated with high direct and indirect costs which may amount to up to $210.5 billion each year [3].

A significant portion of the personal, medical and economic burden entailed by depression stems from its association with a myriad of medical conditions, including various gastrointestinal and metabolic disorders [4] autoimmune disorders [5], cancer [6], and Cardiovascular Disease (CVD) [7], among others; highlighting the tight link between mental and somatic well-being. The association between depression and CVD is especially relevant, as both of these conditions have become worldwide epidemics. At present, CVD is the leading cause of morbidity and mortality globally, accounting for approximately 17.5 million deaths yearly, and representing 31% of all global deaths [8]. Furthermore, up to 15% of subjects with CVD may have comorbid depression [9].

Notwithstanding this epidemiologic outlook, very little has been firmly established regarding the mechanisms underlying this association between depression and CVD, as well as its implications in clinical practice [7]. Nevertheless, emerging views on depression as the result of chronic dysregulation of a systemic stress response may contribute to the bridging of this gap [10]. Indeed, various physiological components of the stress response which are also often found in depressed individuals –such as Insulin Resistance (IR), systemic inflammation and a pro-thrombotic state– are profoundly involved in the pathogenesis of CVD [11]. Therefore, viewing depression in the context of chronic systemic stress may aid in the comprehension of its association with CVD.

Because depressive symptoms may be present in a wide array of psychiatric disorders, such as bipolar disorder, dysthymia, and Major Depressive Disorder (MDD); all of which may be explained by differing etiopathogenic hypotheses, this review will focus on the study of the latter. The objective of this review is to describe the physiologic implications of MDD conceived as a chronic, dysregulated stress response, and their overlap with the pathophysiology of CVD.

Major Depressive Disorder: An Overview

Currently, MDD is considered one of the leading causes of disability worldwide, accounting for approximately 63,200,000 Disability-Adjusted Life Years (DALY), which represents 24.5% of all

DALY, lost to mental disorders, and 2.5% of DALY lost to all diseases [12]. In addition, MDD is a major risk factor for suicide, which may occur in up to 13% of these patients, or an estimate of 1 million deaths every year [13]. Furthermore, all-cause mortality has been observed to be considerably higher in subjects with MDD [14]. Thus, part of the burden attributed to MDD stems from its association with various other mental and physical diseases [15].

Clinically, MDD may feature core affective symptoms, such as depressed mood and anhedonia, as well as cognitive symptoms –thoughts of worthlessness or guilt, thoughts of death or suicide, impaired concentration–, psychomotor symptoms, such as loss of energy and fatigue, and psychomotor retardation or agitation, and vegetative symptoms, such as changes in weight or appetite and insomnia or hypersomnia [16]. The latter are particularly relevant for the definition and differentiation of two classic phenotypes of MDD: Melancholic *vs* atypical depression. Whereas melancholic depression is characterized by weight or appetite loss and insomnia with early morning waking, atypical depression features "inverse vegetative symptoms", with increased weight or appetite and hypersomnia. In addition, atypical depression includes mood reactivity and rejection sensitivity, in opposition to a subjective sense of detachment and pervasive anhedonia in melancholic depression (Figure 1) [17].

Although each of these forms of depression may correspond to particular neurobiological phenomena –discussed in a further section of this article–, views on the pathophysiology of this disorder are currently dominated by the monoamine hypothesis, wherein decreased signaling of serotonin (5HT), Norepinephrine (NE) and Dopamine (DA) in the Central Nervous System (CNS) may account for distinct manifestations of depression [18] (Figure 2). Dysregulation of 5HT signaling in the frontal cortex and basal nuclei is related to symptoms such as anxiety, tearfulness and obsessive-compulsive behaviors, whereas lower NE levels are related to alterations in attention, concentration and other cognitive functions, and disrupted DA signaling corresponds to symptoms such as anhedonia and blunted affect [19]. Although these hypotheses constitute the basis for the current pharmacotherapy of depression, the origin of this "end state" of monoamine signaling dysfunction remains unelucidated and a subject of intense research.

Indeed, the pathogenesis of depression may involve components as diverse as gene mutations, neurotransmitter availability, receptor sensitivity and regulation, and vascular lesions in specific areas of the brain, as well as immune and endocrine dysregulation [20]. Genetic variations associated with various brain metabolic pathways may be relevant, including polymorphisms of the monoamine oxidase gene A [21], group-2 metabotropic glutamate receptor gene (GRM3) [22] and the glucocorticoid receptor gene NR3C1 [23]. Neurotrophin dysfunction in the amygdala, hippocampus, cingulate cortex and medial prefrontal cortex has been associated to MDD [24], in conjunction with impairments in synaptic plasticity and neurogenesis [25]. In particular, these alterations have been closely linked with dysregulation of the Hypothalamic-Pituitary-Adrenal Axis (HPAA) and chronic neuroinflammation [26].

Sustained activity of proinflammatory mediators such as Tumor Necrosis Factor-α (TNF-α) and inteleukin-6 (IL-6) in the CNS has been linked to alterations in neural structure and function secondary to oxidative stress [27] and mitochondrial dysfunction, with significant behavioral correlates in depression [28]. These events may be propitiated, precipitated and perpetuated by both acute and chronic stressors, highlighting the importance of the physiology of the stress response in the understanding of depression.

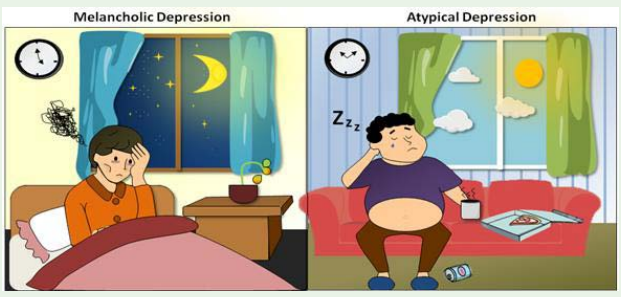

Figure 1: Core differences between melancholic and atypical depression: Whereas melancholic depression features weight loss, early morning waking, and severe anhedonia or detachment; atypical depression features weight gain, hipersomnia and mood reactivity.

The Stress Response: An Illustrious Example of Mind-Body Interaction

In order to preserve life, all living beings require maintenance of homeostasis, a dynamically stable milieu in the face of changing environments. Therefore, each being disposes of a variable array of coping mechanisms, which constitute a stress response. These are deployed upon the presence of actual or perceived threats, termed stressors [29]. In humans, the stress response comprises a complex group of mechanisms, both psychological –with cognitive, behavioral and affective aspects– and somatic, involving all organ systems [30]. In ensemble, these mechanisms tend to promote survival in a classical acute fight-or-flight situation, with physiological changes that optimize nutrient and blood delivery to the brain, the skeletal muscles and distressed body sites, and an inhibition of functions which may be disadvantageous or non-urgent, such as feeding, sleeping, and sexual and reproductive activity [31]. Nonetheless, when prolonged, the stress response may become maladaptive, as it has been proposed to occur in MDD [10].

The stress response is activated by two synergic neurobiological systems, one dominated by Corticotrophin-Releasing Hormone (CRH) signaling, and one dominated by Norepinephrine (NE)

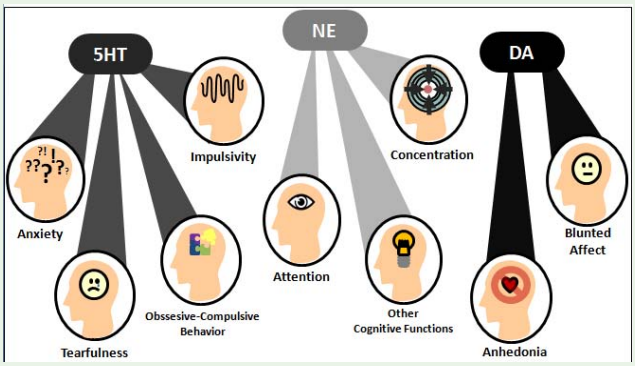

Figure 2: The Monoamine Hypothesis: Decreased signaling by specific neurotransmitters results in disinct psychopathologic manifestations. NE: Norepinephrine, 5HT: Serotonin, DA: Dopamine.

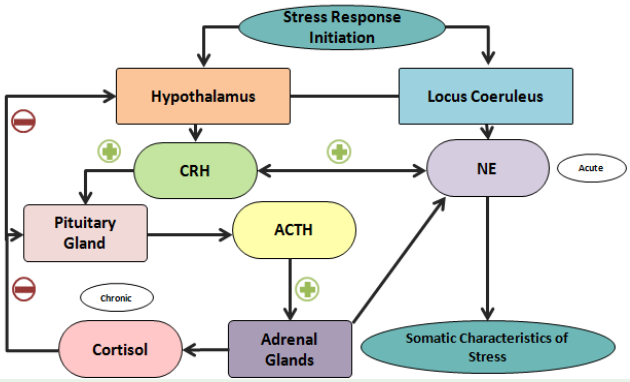

Figure 3: The Stress Response. CRH: Corticotropin-Releasing Hormone, ACTH: Adrenocorticotropin Releasing Hormone, NE: Norepinephrine. The stress response and its somatic characteristics are a result of the activation of the descending sympathetic fibers from the LC, which is reciprocally activated by the CRH system. Cortisol is released via stimulation by ACTH on the adrenal glands after the HPAA is activated by the Hypothalamus.

signaling (Figure 3). The CRH system consists of amygdalar, hypothalamic and peripheral components. The former mediates the activation of fear conditioning and anxious behavior: In mice, deletion of glucocorticoid receptors in the central nucleus of the amygdala has been documented to prevent these behaviors [32]. Moreover, the hypothalamic component of the CRH system consists of a humoral pathway –which induces Adrenocorticotropin-Releasing Hormone (ACTH) in the pituitary, thus activating the Hypothalamus-Pituitary-Adrenal Axis (HPAA)–; and descending, activating projections to the Locus Coeruleus (LC) [33]. Finally, the peripheral component of the CRH system includes CRH-releasing sympathetic nerve terminals. Peripherally, CRH acts as a paracrine mediator of inflammation, and as an autocrine immunomodulator in some immune cells [34].

On the other hand, the NE system is constituted by multiple projections from the LC to the amygdala and hypothalamus, reciprocally activating the CRH system [35]. Along with the effects of HPAA activation, the descending sympathetic fibers stemming from the LC are largely responsible for the systemic somatic characteristics of the stress response. Notably, these include increased cardiac output, a redistribution of blood flow towards key sites for survival and away from splanchnic circulation, promotion of gluconeogenesis, and activation of the innate immune system [36]. Furthermore, exposure to stressors triggers the synthesis and secretion of acute-phase proteins in the liver, including Serum Amyloid A, C - reactive protein, haptoglobin and fibrinogen, all of which favor a systemic pro-inflammatory, pro-thrombotic state [37]. The persistence of this state may be a major contributor to the development of CVD in the context of chronic stress and MDD [38]. Likewise, aspects of gluconeogenesis, such as increased release of free fatty acids and promotion of IR, may be particularly important in the association between chronic stress, MDD and CVD [39].

The cognitive and behavioral aspects of the stress response are the result of interactions between the amygdala, the LC, the Prefrontal Cortex (PFC), the hippocampus, and the Nucleus Accumbens (NA). The PFC is responsible for complex functions, including integration of various sensory modalities, attention, memory, and judgment, among others [40]. The medial PFC is able to restrain activation of the amygdalar system, as well as the HPAA though direct projections to the hypothalamus. In turn, the PFC may be inhibited by NE projections from the LC. Therefore, the interactions between the PFC, the LC and the amygdala dictate the predominance of the superior functions of the PFC or the more survival-oriented behaviors mediated by subcortical structures at any given point [41].

The hippocampus participates in the initiation of the stress response by intervening in the encoding and storing of adverse memories, which may resurface upon exposure to other stressors in a reflexive and unconscious fashion [42]. Because the hippocampus can also regulate activation of the amygdala and the HPAA, the emergence of these data in the hippocampus may trigger a stress response [43]. Lastly, the NA participates in the stress response by keeping a consistent, tonic activation of dopaminergic reward systems, promoted by basolateral amygdalar neural projections [44]. This activity contributes to the stress response by favoring motivation and attention [45].

From chronic stress to depression: A neurobiological slippery slope

Although these neurobiologic mechanisms are a valuable resource for coping with acute stressors, they appear to be comparatively inefficient regarding chronic stress, with both structural and functional neural alterations resulting in maladaptive responses [29]. Indeed, these pathways provide a framework for the understanding of MDD as a chronic disruption of the stress response. This model may be applied more readily to the classic model of melancholic depression: Elevated NE levels in the Cerebrospinal Fluid (CSF) and hypercortisolism, appear to be more frequent in subjects with this diagnosis, indicating sustained activation of the amygdala-LC and PFC-HPAA systems [46].

On the other hand, atypical depression has been associated with exaggerated negative feedback regulation of the HPAA, which has also been observed to occur in chronic fatigue [47]. These states have been associated with hypermethylation of the NR3C1 gene, which results in increased expression of Glucocorticoid Receptors (GR), enhancing negative feedback of the HPAA, and favoring hypocortisolism [48]. Similar findings of altered GR function have been described in other fatigue and pain disorders [49]. This hypothesis harmonizes with the relatively strong hereditary pattern of atypical depression, which has shown higher concordance in monozygotic twins than the melancholic variant [50]. In addition, atypical depression is more often associated with inflammation and metabolic abnormalities, including elevated levels of C-Reactive Protein (CRP), IL-6 and TNF-α, as well as overweight, obesity and dyslipidemia [51]. Thus, proinflammatory cytokines released by adipose tissue may be particularly important in the pathogenesis of atypical depression [52], possibly by modifying expression of GR and other mediators within the HPAA [53].

In contrast, the distinct neurobiological features of dysthymia – termed Persistent Depressive Disorder in the DSM-5 [16] – remain relatively unknown. This disorder describes cases of continuous and prolonged depressive mood, and is generally assumed to be on a shared neurobiological spectrum with MDD, differing only in severity and duration [54]. Epidemiological data appears to support this assumption, as an estimate of 75% of patients with PDD meet the

criteria for a major depressive episode at least once over their lifetime [55], and the risk for relapse into a subsequent episode has been estimated at 71.4% in these subjects, most commonly within three years [56]. Nevertheless, certain differences have been determined: Patients with PDD show reduced activation of the dorsolateral PFC, with increased activation of the amygdala, anterior cingulate cortex and insula [57].

Although scarce to date, these distinct neurobiological findings across different types of depression underline the limitations of current diagnostic classifications for mental disorders, which although valuable for practical assessment, may be unable to reflect the neurobiological and clinical nuances of various types of depression. Indeed, depression should be understood as a clinical syndrome with multiple possible etiologies [58], and further research is essential for this characterization and the optimization of therapeutic alternatives.

Chronic Stress, Depression and Cardiovascular Disease: A Pathophysiologic Continuum?

Many putative biological mechanisms have been proposed to underlie the relationship between depression and CVD, including chronic low-grade inflammation, IR, and dysregulation of thrombogenesis [7]. Interestingly, these phenomena are hallmarks of stress responses, which allow the framing of chronic stress, depression and CVD within a single unique pathophysiologic continuum. These mechanisms are further discussed in the following paragraphs.

Chronic inflammation

Depression has been notoriously related with significant changes in immune function, most prominently regarding circulating levels of proinflammatory cytokines. Indeed, Happakoski et al. [59] and Dowlati et al. [60] among others have ascertained higher levels of TNF-α, IL-6 and other cytokines in subjects with depression in broad meta-analyses. Similarly, in a large sample of 73,131 adults, Wium-Andersen et al. [61] found greater levels of circulating CRP –a pivotal mediator in the acute-phase response [62]–to predict risk for hospitalization with depression.

The role of inflammation in the pathogenesis of MDD has been encapsulated in the pathogen-host defense hypothesis, which profiles depression as a form of the classical sickness behavior observed in a wide range of species. Thus, from an evolutionary perspective, depression would encompass the behavioral manifestations of a systemic response to psychosocial stress, in contrast to virulent microorganisms in a classical pathogen-host disease model [11]. Indeed, patients with MDD exhibit numerous key features of systemic inflammatory responses, such as upregulation of various cytokines and chemokines and their receptors, and elevated levels of acute-phase reactants, and cellular adhesion proteins, in both peripheral blood and Cerebrospinal Fluid (CSF) [63].

Inflammatory signals may be relayed to the brain via three chief mechanisms: (A) A humoral pathway, wherein proinflammatory cytokines are able to cross certain regions of the Blood-Brain Barrier (BBB), in particular, circumventricular areas. (B) A neural pathway, where cytokine signaling in afferent neural endings, such as in the vagus nerve, promotes monoaminergic metabolism disruption in the central nervous system. (C) A cellular pathway, where circulating TNF-α synthesis of CC-chemokine ligand 2 in microglial cells, activating chemotaxis of monocytes in the brain. Post-mortem evaluation of suicide victims has revealed increased perivascular macrophages in the brain, with enhanced expression of Allograft Inflammatory Factor 1 (AIF1) and CCL2, which are associated with macrophage activation and cellular transport [64].

In addition, IFN-γ signaling promotes expression of indoleamine (2,3)-dioxygenase, which catalyzes conversion of tryptophan –the precursor amino acid of 5HT– to kyneurenine, which may then be converted to Quinolinic Acid (QA) [65]. The latter is a neurotoxic metabolite which can activate microglia and promote monocyte and macrophage infiltration to the brain. QA can also directly activate glutamate receptors and inhibit glutamate reuptake by astrocytes. The resulting hyperactivation of NMDA receptors may result in excitotoxicity and decreased production of Brain-Derived Neurotrophic Factor (BNDF), a key target for antidepressant activity. High levels of QA have been found in the anterior cingulate cortex of suicide victims [66].

Furthermore, proinflammatory cytokines reduce synaptic availability of monoamine neurotransmitters through a myriad of mechanisms, possibly representing a fundamental link in the pathogenesis of MDD. Induction of Mitogen-Activated Protein Kinase (MAPK) expression by IL-1β and TNF-α has been associated with augmented expression and function of 5HT reuptake transporters and decreased 5HT availability. Likewise, inflammation-related generation of reactive oxygen species and cytokine signaling is associated with diminished tetrahydrobiopterin (BH4) availability, an enzymatic cofactor essential for synthesis of all monoamines [63]. Similarly, high levels of proinflammatory cytokines and C - reactive protein have been linked to hypoactivation of the basal nuclei, in particular the ventral striatum and substantia nigra, in association with decreased responses to rewards and augmented susceptibility to negative reinforcement [66,67]. In addition, increased inflammatory signaling has been linked to hyperactivity of fear-related neurocircuits, especially in the anterior cingulate cortex, insula and amygdala [68].

In parallel to these pathways from systemic inflammation to depression, psychosocial or physiologic stress may also trigger inflammation, possibly constructing a positive feedback loop. Psychophysiological stress has been observed to induce expression of endogenous Damage-Associated Molecular Patterns (DAMP) and NLRP3-containing inflammasomes, which are responsive to DAMP. Likewise, upon stress, non-pathogenic commensal bacteria found in the gut may enter the peripheral bloodstream, whose Microbial-Associated Molecular Patterns (MAMP) may also activate inflammasomes [63]. This activation triggers glucocorticoid resistance in inflammatory cells, possibly potentiating their activity in the brain, contributing to the pathogenesis of MDD. Increased expression of NLRP3, as well as caspase 1 in blood mononuclear cells, has been related to increase circulating levels of IL-1β and IL-18, in correlation with depression severity [67].

Insulin resistance

Several studies have demonstrated the link between IR and depression [69,70]. In a longitudinal study that included 2316 adult women, Everson-Rose et al. [71] found depressed subjects to have greater IR prevalence, as well as higher risk of type 2 Diabetes Mellitus (DM2). Similarly, levels of IR have been described to vary

proportionally to the severity of depression [72], a relationship which may be mediated, at least partially, by adiposity and waist circumference [73].

Many neuroendocrine phenomena predispose to the development of IR in depression: Notoriously, HPAA activation results in elevated cortisol levels, which increases hepatic gluconeogenesis, inhibits pancreatic insulin secretion, and facilitates ectopic fat deposition in the liver and skeletal muscle, which ultimately renders these tissues less sensitive to insulin signaling. In parallel, hypercortisolemia appears to promote adipogenesis while simultaneously favoring lipolysis, resulting in increased and sustained release of free fatty acids, which in turn may powerfully promote IR in the liver. In addition, enhanced cortisol activity may lead to expansion of intravascular volume, contributing to hypertension [74].

On the other hand, prominent pro-inflammatory cytokines in depression, such as IL-6 and TNF-α, can hinder insulin signaling by triggering phosphorylation of the serine/threonine residues on the Insulin Receptor Substrate (IRS-1) [75]. IL-1β activity has also been linked with decreased IRS-1 expression [76]. In ensemble, these alterations lead to decreased glucose uptake in the classic insulin dependent tissues –chiefly, the liver and skeletal muscle– which in turn favors glucose availability for non-insulin dependent tissues, such as the brain and immune cells. In this scenario, IR has been conceived as a key component in the physiological response to a myriad of stressors, by differentially promoting glucose delivery to essential sites [10]. Nevertheless, chronic IR, as found in depression, has been associated with multiple pathophysiologic phenomena, such as atherosclerosis, endothelial dysfunction and left ventricular hypertrophy, all of which predispose to CVD [75].

Dysregulation of thrombogenesis

Depression has been linked to alterations in endothelial function in healthy subjects and those with established CVD [77], with relevant clinical correlates: Paranthaman et al. [78] have described significant changes in vascular function in depressed individuals, including greater carotid intima media thickness and pulse wave velocity, as well as blunted responses to acetylcholine in preconstricted small arteries. Similarly, Williams et al. [79], found patients hospitalized for acute coronary syndrome and moderate depression to have higher levels of circulating TNF-α, IL-6 and C - reactive protein, as well as enhanced ADP-induced platelet aggregation. Most strikingly, depression has been associated with worse prognosis and greater recurrence of cardiovascular events [80].

Several pathogenic mechanisms have been proposed to explain the aforementioned findings. Dysfunctional polymorphisms of the Brain-Derived Neurotrophic Factor (BDNF) gene, which have been linked with increased susceptibility to depressive and anxious disorders, appear to co-occur with a myriad of prothrombotic phenomena [81]. Notably, in rats, Amadio et al. [82] have described the dysfunctional BDNF Met/Met polymorphism to be associated with lower size, volume and quantity of platelets and reticulocytes, higher levels of α1-antitrypsin, and IL-6, as well as worse erythrocyte sedimentation rates and greater leukocyte recounts, especially monocytes and neutrophils, reflecting a proinflammatory and prothrombotic state. In this study, these alterations resulted in shorter mean time to total occlusion in induced carotid artery thrombogenesis models.

Subjects with depression have also been described to show elevated levels of β-thromboglobulin and platelet factors, as well as increased expression of P-Selectin and glycoprotein IIb/IIIa [83]. Likewise, hyperactivation of the HPAA with hypercortisolemia has been linked to down regulation of endothelial nitric oxide synthase [84], while peripheral CRH signaling may upregulate expression of macrophage-1 antigen and release of endothelin from monocytes. These disruptions result in diminished endothelial nitric oxide synthesis, leading to endothelial dysfunction and contributing to increased cardiovascular risk [85]

Conclusion

As has been revealed by recent research, the neurobiology of chronic stress and depression appear to be on a pathophysiologic continuum with cardiometabolic disease, with severe repercussions in individual productivity and quality of life. Nevertheless, further in-depth study is required in order to ascertain the relative importance of different components in this pathophysiologic framework, in regards to impact in overall well-being and potential to serve as novel therapeutic targets. In particular, chronic inflammation and IR appear to be attractive targets, acting as powerful links in the relationship between mental and somatic ailment. In this context, recent state-of-the-art studies have assessed alternatives such as monoclonal antibodies [86], non-steroidal anti-inflammatory drugs [87] and metformin [88]. Indeed, the field of depression therapeutics appears promising, in light of the increased scientific and social interest experienced in this area in recent decades.

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