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 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.

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
The Monoamine Hypothesis: Decreased signaling by specific neurotransmitters results in distinct psychopathological manifestations. NE: Norepinephrine, SHT: Serotonin, DA: Dopamine.

of various sensory modalities, attention, memory, and judgment, the Cortex (PFC), the hippocampus, and the Nucleus Accumbens (NA). The result of interactions between the amygdala, the LC, and the Prefrontal Cortex (PFC) is the predominance of the superior functions of the PFC or the more survival-oriented behaviors mediated by subcortical structures at any given point.

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. 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. Lastly, the NA participates in the stress response by keeping a consistent, tonic activation of dopaminergic reward systems, promoted by basolateral amygdalar neural projections. This activity contributes to the stress response by favoring motivation and attention.

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. 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 hypocortisolism, appear to be more frequent in subjects with this diagnosis, indicating sustained activation of the amygdala-LC and PFC-HPAA systems.

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. 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. Similar findings of altered GR function have been described in other fatigue and pain disorders. This hypothesis harmonizes with the relatively strong hereditary pattern of atypical depression, which has shown higher concordance in monozygotic twins than the melancholic variant. 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. This hypothesis harmonizes with the relatively strong hereditary pattern of atypical depression, which has shown higher concordance in monozygotic twins than the melancholic variant.

In contrast, the distinct neurobiological features of dysthymia—termed Persistent Depressive Disorder in the DSM-5—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. Epidemiological data appears to support this assumption, as an estimate of 75% of patients with PDD meet the criteria for MDD.

[Diagram: Stress Response]
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 kynurenine, 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 (BDNF), 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, hypercortisolism 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 counts, 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 hypercortisolism 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 ailments. 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.

References


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