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Review

Role of Platelets in Connecting Depression with Cardiovascular Diseases – A Brief Review of Current Literature

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ABSTRACT

Cardiovascular diseases (CVD) are known to be the most common cause of death worldwide and have long been associated with various psychosocial factors. Depression on the other hand is conceptualised as a systemic illness with neurobiological mechanisms overlapping with various medical disorders including cardiovascular and related diseases. The comorbidity between depression and coronary heart disease is a recognised risk factor for cardiac events including mortality. The relationship between the two however, is multifaceted and seen to be bidirectional as per existing research. Although the exact underlying mechanisms remain poorly understood, several diverse processes such as neuroendocrine dysregulation, inflammation, and autonomic system and platelet activity alterations have been proposed to play a role in complicating the prognosis of comorbid depression and CVD. This article focuses on reviewing current literature to study recent evidences and explore the dynamics between these two disorders through the mediation of platelets.

KEYWORDS: Platelets, Depression, Serotonin, Cardiovascular

INTRODUCTION

As per World Health Organisation, cardiovascular diseases (CVD) remain the most common cause of death globally and an important target for health reforms. Amongst psychosocial factors in CVD, the role of specifically depression is multifaceted and found to be bidirectional[1]. Studies have not clearly deciphered if this association could be causative or only temporally related. Behavioural factors along with activation of the hypothalamo-pituitary and adrenal (HPA) axis, dysregulation of autonomic, serotonin and neurotrophic pathways, oxidative stress, and platelet activation with endothelial dysfunction are the various proposed underlying mechanisms[2-7]. Depression, now conceptualized as a systemic illness with varied neurobiological mechanisms explaining its influence on other medical illnesses, increases the risk of and accelerates the progression, and gives poorer treatment response for numerous medical disorders, including cardiovascular[8].

This article intends to summarise the various factors involved in the intricate dynamics of CVD and depression and review the recent literature findings outlining the specific role of platelets in the same. The relationship between the medical and psychiatric aspects of this disorder is discussed under domains of overlapping endocrine,

behavioural ang genetic components as well as the many proposed neurochemical mechanisms. The role of platelets via serotonin pathways is specifically mentioned along with potential biomarkers indicating further research directions.

FINDINGS

Relationship between CVD and Depression

Many investigators studying potential biological and behavioural explanations for increased association between CVD and Depression mention several plausible potential mechanisms. These include behaviours like medication noncompliance, cigarette smoking, and physical inactivity, apart from biological factors[9,10]. The coexistence of these two conditions is more lethal than either diagnosis alone[11,12].

HPA axis in CVD and Depression

Chronic or severe stress activates HPA axis through CRF (corticotropin releasing factor) induced glucocorticoid activation and thus causes hyperglycaemia. This results in insulin resistance, leading to diabetes mellitus with potential cardiovascular events[13]. Elevated CRF stimulates the production of IL-1, IL-6, and TNF-alpha (pro-inflammatory cytokines) by immune cells in bloodstream, which cross blood-brain barrier, causing neuroinflammation, and producing depression-like symptoms[14].

Lifestyle in CVD and Depression

Patients with depression commonly exhibit a lifestyle which involves use of alcohol, cigarette smoking, junk food, poor compliance to medication, and reduced physical activity. This results in significant weight gain, and poor resultant health outcomes. These patients are less likely to change their lifestyle towards adoption of healthy behaviours[15]. Literature shows the mportance of higher calorie foods containing saturated fat, energy drinks and high glycemic foods to cause a rise in peripheral inflammatory markers. On the other hand, a diet of fruits, vegetables, and high fibre reduces inflammation, free radical production and the levels of pro-inflammatory cytokines[16].

Genetics in CVD and Depression

The genetic association between these two ailments is mediated through the interaction of brain derived neurotrophic factor (BDNF) and steroid hormones (stress-induced glucocorticoid elevation). Recent literature states that glucocorticoids reduce the BDNF-dependent upregulation of excitatory glutamate receptors by suppressing microRNA-132 expression. This is thought to play a role in the pathophysiology of various neurological diseases including psychiatric disorders, Alzheimer's disease, and Parkinson's disease[17].

Platelets

Platelets are known to be an essential component of our haemostatic process with additional physiological and immunomodulatory roles[18]. Biochemical agonist binding (collagen, thrombin, arachidonic acid, epinephrine) or disruption of blood vessels mechanically causes the initiation of haemostatic responses in local vascular endothelium. This causes the start of thrombus formation where platelets adhere to the damaged endothelium, become activated, and aggregate together, followed by serotonin granule secretion into extracellular space. This process is mediated through intracellular chemical signals (P selectin and glycoprotein IIb/IIIa)[19].

Serotonin

Evidence supports that serotonin (5-HT) plays a key role in the psychopathology of depression. The cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of 5-HT is found to be low in suicidal patients[20]. A whopping 99% of the body's serotonin is stored in the dense granules of platelets[21]. Release of serotonin from these granules at the damaged endothelial sites plays a major role in promoting aggregation of platelets during thrombus formation. This gives a logical mechanism of how platelets link depression with CVD[22].

Platelets in Depression

Depressed patients have been shown to exhibit increased reactivity, and increased P selectin and activated glycoprotein IIb/IIIa expression in platelets[23]. Thus, increased susceptibility for platelet activation looks to be a possible mechanism behind depression posing as a significant risk factor for CVD. The popular SADHART trial examined the effects of sertraline (SSRI-selective serotonin reuptake inhibitor) treatment for 24 weeks in patients with acute coronary syndrome and depression. It found that SSRIs supress platelet activation (based on diminished release of P-selectin and β thromboglobulin from platelets)[24].

Other platelet pathways seen to exhibit significant changes in depressed patients are reduction in platelet adenosine response, increase in platelet thrombin response, increase in expression of glycoprotein Ib, and decrease in BDNF levels in platelets[25]. Several other molecular mechanisms interlinked with the physiological functioning of platelets and potentially contributing to increased aggregability are discussed below.

Platelets and Catecholamines

Platelets express dopaminergic as well as adrenergic receptors, modulating thrombopoiesis through them. Low level of serum catecholamines potentiates the effects of thrombin and collagen (coagulation agonists). High serum catecholamines can independently induce platelet aggregation, and secretion of granules along with release of platelet markers (beta-thromboglobulin (BTG) and Platelet Factor 4 (PF4))[26].

Platelets and Leptin

Peptide hormones receptors (long form of leptin receptor (LEPRL)) on platelet surface underlies the link between altered leptin levels in depression and possibly altered platelet response contributing to cardiovascular complications. Leptin is known to increase thrombotic processes by potentiating platelet aggregation, and increasing platelets adhesion[27].

Platelets and Adiponectin

Adiponectin receptors (AdipoR1 and AdipoR2) on platelet surface has also been found in mice, where deletion of adiponectin increased thrombus formation in arterial injury induced photochemically. Anti-thrombotic effect of adiponectin seems to be related to leukocytes (reduced titre of aggregates of polymorphonuclear leukocytes/ or monocytes with platelets), and the inhibition of macrophage-related Tissue Factor (TF), which impairs coagulation cascade[28,29].

Platelets and Neurotrophins

Platelets contain both Nerve Growth Factor (NGF) and BDNF. While NGF can induce aggregation by binding to platelet surface, binding of BDNF can cause internalization of specific receptor sites[30].

Platelets and Low-Density Lipoprotein

Lipid alterations contribute to acute thrombotic events through platelet activated thrombosis. Low Density Lipoproteins are seen to increase platelet sensitivity to stimulation from agonists which makes them to respond faster and more extensively[31].

Platelets and Reactive Oxygen Species (ROS)

Extracellular ROS is known to promote thrombotic events. Activated platelets generate ROS which in turn activate more platelets. Intracellular ROS in platelets promotes secretion of dense exocytosis and increases platelet receptor sensitivity[32].

Serotonin in Haemostasis and Thrombosis

The role of platelets in haemostasis and thrombus formation is undisputed. Serotonin influences platelets in multiple pathways, including their binding at von Willebrand-Factor (vWF) on damaged endothelial sites in the vasculature. Platelets adhere on vWF via their surface glycoprotein (GP Iβα). This allows collagen to interact with GP IIb/IIIa further allowing intracellular signalling and dense granule exocytosis[33].

SSRIs have been shown to play a role venous thrombotic phenomenon. Depressed patients have reported higher incidence of venous thromboembolism (VTE). Also, the clinical use of tricyclic antidepressants other antidepressants is independently seen to be associated with increased risk of VTE[34,35].

BDNF

Evidence suggests BDNF may be useful as a biomarker in depression for the purpose of diagnostic clarity and prognostic implications[36]. Platelets – a major source (99%) of peripheral BDNF, are important for mediating the survival and activation of endothelial cells and playing a role in angiogenesis[37,38]. Low levels of BDNF are seen in patients with major depressive disorder and these levels have been shown to increase with long term antidepressant treatment. Increasing evidence has reiterated the presence of prothrombotic endophenotype in patients suffering from depression. Some authors have proposed the occurrence of epi-phenomenon (upregulation of BDNF receptors) resulting in altered BDNF metabolism and/or variation in peripheral BDNF titres during treatment with antidepressant medications in patients of depression[39,40].

CONCLUSION

Recent literature findings reiterate the fact that platelet dysfunction is a major connecting link between depression and cardiovascular pathology, contributing to increase in morbidity and mortality. Despite substantial evidence, the complex molecular mechanisms and mediators involved in this process need to be disentangled in order to formulate clear and robust associations with each other. There is an interesting role of neurotropic factors in possible epigenetic modulation affecting gene expression and subsequent presentation of depression in medical illnesses.

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