MAJOR DEPRESSIVE DISORDERS AND CORONARY ARTERY DISEASE: A REVIEW ON COMMON PATHOPHYSIOLOGICAL PATHWAYS

Giulia Ida Perini, Arianna Di Florio, Chiara Pavan

Abstract

Patients with Major Depressive Disorder (MDD) have an increased risk of developing or worsening coronary artery disease (CAD). The pathophysiology of this increased risk is only partially understood: six different but not opposing hypotheses have been proposed, involving hypothalamic pituitary adrenal axis (HPA) and autonomic nervous system (ANS) dysregulation, platelet activation, endothelial dysfunction, inflammation and behavioural factors, including treatment adherence and lifestyle habits.

A simple model, based on a link between depression and bio-behavioural alteration, seems oversimplified and is not supported by data. Moreover, the link between coronary artery disease and depression represents the typical "chicken-egg" dilemma. Epidemiological studies clearly show that MDD or depressive symptoms are risk factors for CAD; conversely, CAD induces a depressive syndrome in 20-47% of acute cases, suggesting that MDD and CAD may share common pathophysiological pathways.

In this review we attempt to unify the five above-mentioned mechanisms and propose that a central alteration could represent a link between depression and coronary artery disease, altering the peripheral response to stress via the HPA-axis, ANS, an immune response and platelet function. The relevant literature was sought through MEDLINE, PubMed, PsycINFO and EMBASE. The following search words were used alone or in combination, as appropriate: depression, myocardial infarction, coronary artery disease, endothelial dysfunction, inflammation, neurobiological aetiology. Further articles were sourced from the reference lists of articles ascertained through the search.

Key Words: Major Depressive Disorder – Coronary Artery disease – Autonomic Nervous System – Hypothalamic Pituitary Adrenal Axis

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Introduction

Major Depressive Disorder (MDD) is a common clinical condition, with high lifetime prevalence in the general population, and is associated with a very high level of disability (ESEMeD 2004). Both primary unipolar and bipolar depression are chronic, highly recurrent disorders with strong neurobiological and genetic roots. The interplay of a genetic disposition, based on small contributions from several genes involved in the regulation of neuronal development, functioning and plasticity, together with environmental determinants of stressful, neurotoxic events (losses, psychic and physic trauma) and/or lack of positive, neuroprotective factors (cognitive and emotional positive stimulation, physical exercise, etc.), is the framework for a deeper understanding of the aetiology, neurobiology, course prognosis and treatment of MDD. Once a major depressive episode takes place, the profound neurobiological and physical changes that occur will affect the future course of the disease, determining the frequency, severity and therapy response to common treatment of further episodes.

Major depressive disorder (MDD) is an independent risk factor for increased mortality (Carney et al. 2008; van Melle et al. 2004; Barefoot et al. 1996; Frasure-Smith et al. 1993, 1995; Bush et al. 2001) in patients with cardiovascular disease and a predictor for developing coronary artery disease (CAD) (Rugulies 2002, Lett et al. 2004); CAD is a risk factor for the development of depression (Schleifer et al. 1989, Frasure-Smith et al. 1993, Sorensenf et al. 2005, Bush et al. 2005). Although the results of some studies contrast with these epidemiological observations (Lane et al. 2002, Stewart et al. 2003), depression is a risk factor for cardiovascular morbidity (van der Kooy et al. 2007, Wulsin et al. 2003). ⁻One review indicated that depression conferred a relative risk of between 1.5

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and 2.0 (Lett 2004) for the onset of CAD in healthy individuals, while the prevalence of major depression was about 20% in patients hospitalised for acute myocardial infarction (AMI) and an additional 10- 47% of AMI subjects reported symptoms of depression (Bush et al. 2005). Moreover, the relative risk for death in depressed AMI patients is 2-2.5 times greater than in non-depressed AMI patients (van Melle et al. 2004). This heightened risk is also maintained in the long term (> 2 year) and is independent from other risk factors (Barth et al. 2004).

Several underlying causative mechanisms are possible. Many bio-behavioural alterations, which could explain the epidemiological data, have been already identified, both in depressed patients with CAD and in patients with depression or CAD.

The literature (Barefoot 1996) usually reports six different hypotheses, involving the hypothalamic pituitary adrenal (HPA) axis, the autonomic nervous system (ANS), platelet activation, endothelial dysfunction, inflammation and behavioural factors, including treatment adherence and lifestyle habits. However, a model based on a simple link between depression and bio-behavioural alteration, seems oversimplified and is not supported by data. Moreover, the link between CAD and depression represents the typical "chicken-egg" dilemma. Indeed, it has not been yet clarified whether depression comes before or after the biochemical alterations related to CAD or whether CAD and depression share some common pathophysiological pathways, without a causative link.

Irani (2005) proposed that a primary defect in the prefrontal cortex (PFC) of depressed subjects alters the autonomic neuro-cardiac balance and could be considered the "primum movens" linking depression to CAD. However, apart from PFC, there are many other structures in the central nervous system (CNS) involved in both the pathogenesis of depression and cardiac stress response. Growing evidence, from neuroendocrine testing, brain imaging and pathological studies of subjects with MDD, suggests that emotional and stress response systems, including the amygdala, are pathologically activated in MDD and are associated with abnormalities in PFC and monoamine neurotransmitter systems that modulate behavioural and emotional responses (Gold et al. 2002, 2005; Drevets 2003).

In this review we try to unify the six mechanisms mentioned above, in order to propose that a central alteration in mood-relevant neurocircuitry, including the amygdala, hippocampus and PFC, could represent a link between depression and CAD, altering the peripheral response to stress via the HPA-axis, ANS, immune response and platelet function. Moreover, mesocortical pathway alterations might also explain depressed patients' greater exposure to some traditional risk factors for AMI (smoking, diet, exercise, poor compliance, social isolation).

The search in MEDLINE, PubMed, PsycINFO and EMBASE identified relevant literature databases. The following search words were used alone or in combination, when appropriate: depression, myocardial infarction, coronary artery disease, endothelial function, inflammation and neurobiological aetiology. Further articles were sourced from the reference lists of articles ascertained through the search.

Stress and depression

The term "homeostasis" defines the tendency of a living organism towards stability, which is challenged by stressors, i.e. intrinsic or extrinsic forces that threaten the body's equilibrium. Stressors are not necessarily negative: mild and brief stimuli, called "eustress", may improve the organism's development. Conversely, persistent, uncontrollable challenges, called "distress", lead to maladaptative responses (Charmandari et al. 2005), as first described in 1936 by Selye (Selye 1998), who introduced the concept of the "general adaptation syndrome". This includes three successive phases: alarm reaction, resistance and exhaustion. Sterling and Eyer (McEwen 1998) defined the ability to achieve "stability through change" as "*allostasis,*" and McEwen and Stellar (1993) referred to the condition of dysfunction of allostatic systems as *"allostatic load*". The general adaptation syndrome leads to the biological notion that stress response, involving endocrine, neuroendocrine, autonomic, CNS and immune system activity, begins in the brain and affects both the brain and the rest of the body, including the cardiovascular system (McEwen 2007, 2008).

Psychosocial stress is a trigger for the development of psychiatric disease, particularly depression (Gold et al. 1988a, 1998b, 2002, 2005), and stressful events contribute to the development and recurrence of depressive episodes (Kendler et al. 1999, Post 2007). Moreover, immune, CNS and endocrine mediators of stress response may be involved in the pathogenesis of major depression. All these features are modulated by genetic factors that contribute to the risk of developing stress-related depression. Recently, a twin study estimated that genetic factors explain 12% of individual differences in affective response to stress, while individual-specific environmental factors explain the remaining 88% (Jacobs et al. 2006).

Two distinct clinical depressive syndromes have been identified, based on the different patterns of neurovegetative and cognitive symptoms: melanchonic and atypical depression (Gold et al. 2002). Melanchonic patients exhibit a state of pathologic hyperarousal. Cognitive symptoms are intense anxiety, prevalence of painful emotional memories, helplessness, decreased concentration; neurovegetative symptoms include insomnia (most often early morning awakening), loss of appetite, diminished libido, suppressed reproductive and growth hormone axis, increased HPA activity with increase glucocorticoid and norepinephrine levels, dyslipidemia and insulin resistance. These features are related to a dysfunction of stress response systems, both central and peripheral, and may alter the cardiovascular system. Atypical depression is an anergic, lethargic depression with increased need for sleep and food, especially carbohydrates, and thus increased BMI and visceral fat. The HPA axis in these patients is hypoactive as in the exhaustion state described by Seyle (Gold et al. 2002).

Neuronal pathways in stress response involved in major depression

Integrative centers

Integration of a widely distributed limbic/paralimbic (amygdala, hippocampus and PFC) neural network plays a central role in behavioral and neuroendocrine stress response regulation. Thus, abnormalities in the activity of integrated circuits may be responsible for both depressive symptoms and cardiovascular diseases (mainly due to the peripheral effects of hypercortisolism and norepinephrine dysregulation), and represent an important link between depression and CAD.

Amygdala

The amygdala stimulates the HPA axis and glucocorticoids (GC) stimulate the amygdala (Herman et al. 2005). A high concentration of glucocorticoid receptors has been reported in the amygdala in the post-mortem brain (Sarrieau et al. 1986). Hypercortisolism may consequently cause amygdala overactivity that reciprocally leads to hypersecretion of cortisol. Moreover, the amygdala may be involved in the dysregulation of the HPA axis, observed in major depression (Holsboer et al. 1994). It has been shown that left amygdala metabolism is positively correlated with the severity of depressive symptoms, cortisol plasma levels and the risk of relapse during remission. During treatment with antidepressants, amygdala metabolism decreases in treatment responders and HPA activity normalizes in treatment responders only (Drevets et al. 2002). Depression and anxiety share overactivation as the common pathophysiological mechanism in genetically predisposed carriers of short allele serotonin transporter gene-linked polymorphism (5-HTTLPR-S), during processing of emotional stimuli related to neutral stimuli (Munafò et al. 2008).

Prefrontal cortex

PFC plays a key role in the stress response, by regulating neuroendocrine and autonomic responses (Cerqueira et al. 2008). PFC inhibits the amygdala through GABAergic neurons (Davidson et al. 2000). In normal conditions, the PFC inhibits sympathetic nervous system (SNS) activity, promoting the parasympathetic (PS) function. Conversely, during dangerous situations, PFC hypo function fails to tonically inhibit the SNS, potentially activating the "fight or flight" response. The left PFC also inhibits the stress response mediated by the HPA axis and ANS. Hence, dysfunction in the left medial PFC causes a lack of inhibition in the right medial PFC, altering neurovegetative functions (Drevets 2000).

Alterations in PFC have been observed in patients with MDD. Neurophysiologic and neuroimaging studies have shown reduced volume and cerebral blood flow in the PFC of depressed patients (Drevets 2000). Depressed subjects exhibit morphological and functional alterations of PFC, which impair regulation of neurovegetative functions, including those related to the cardiovascular system. Accordingly, a primary deficit in the PFC, as observed in depressed patients, results in autonomic cardiac imbalance (increased SNS/decreased PS activity) and may account for some of the adverse effects of depressive symptoms on CAD, as decreased heart rate variability (HRV) and increased risk of arrhythmias (Irani 2005).

The prefrontal cortex also seems to be involved in modulation of the immune response. Correctly balanced activity of both hemispheres contributes to proper immune system functioning. It has also been shown that selective activation of the left hemisphere leads to a general pattern of immunopotentiation, while the right hemisphere is involved in immunosuppression (Cerqueira et al. 2008).

Hence, PFC participates not only in autonomic and emotional modulation, but also in immune response, representing a double link between central MDD and peripheral CAD.

Hippocampus

The "neurogenesis hypothesis of depression" is based on the theory that failure of adult hippocampal neurogenesis may sustain mood and cognitive and neuroendocrine symptoms of MDD (Kempermann and Kronenberg 2003). Several converging lines of research support this theory (Duman and Monteggia 2006, Campbell and McQueen 2004). Another interesting aspect of this hypothesis is that it links alteration of integrated stress responses, hypercortisolism and ANS to increased risk of CAD. The "glucocorticoid cascade hypothesis" (Sapolsky 1986) suggests that abnormalities in hippocampal functions affect CRH hypothalamic release, leading to elevations of glucocorticoid levels, while hypercortisolism, which has a neurotoxic and neurogenesis-inhibiting effect, progressively reduces hippocampal inhibition on the HPA axis (Mirescu and Gould 2006). This implies that the hippocampus is primarily involved in allostatic load. According to this hypothesis, under repeated or chronic stress, adaptive and protective responses to stress become maladaptive and provoke neuronal hippocampal damage: this damage is responsible for a further increase in glucocorticoids levels (McEwen 2001, 2008). Inflammation may be another link between CAD and hippocampus, modulating adult hippocampal neurogenesis. Pro-inflammatory mediators seem to disrupt the critical balance of the neurogenesis pattern in the hippocampus and to inhibit the migration of stem cells to the proper site (Das and Basu 2007). All these neurotoxic and neurogenesis-inhibiting processes converge and may be responsible for progressive, increasing 'scarring' of the hippocampus after each episode. This could constitute the neurobiological basis for the kindling-like, recurrent course of MDD (Post 2007, Perini et al. 2004).

Antidepressant therapy, positive cognitive stimulation and physical exercise all have neuroprotective effects on hippocampal neurogenesis, counteracting the neurotoxic effects of stress (Duman and Monteggia 2006). A neuroprotective role for endogenous neurothrophic factors, such as BDNF and

vascular endothelial growth factor (VEFG), as endogenous mediators of antidepressant action through induction of hippocampal neurogenesis, have been demonstrated by several *in vitro* and *in vivo* preclinical studies (Warner-Schmidt and Duman 2006). VEFG could be a promising molecular link between depression and cardiovascular disease and become a biomarker for subtypes of depression linked to CAD (Warner-Schmidt and Duman 2008).

Effectors links

Autonomic Nervous System (ANS)

Although the heart has an intrinsic automaticity, provided by different cardiac tissues with pace-maker properties, the ANS modulates the electrical and contractile activity of the myocardium, through the balance of SNS and parasympathetic nervous system (PS, vagal) outflows, which have opposing actions on cardiac pacemaker cells. While vagal stimulation causes hyperpolarisation and decreases the rate of depolarisation, sympathetic stimulation increases it, producing a positive chronotropic effect (Sztajzel 2004). Hence, heart rate reflects autonomic balance and is a simple method of investigating ANS activity. In particular, heart rate variability (HRV), expressing the total amount of instantaneous RR intervals on electrocardiographic registration, is a non-invasive marker of autonomic activity. The HRV decreases when the sympathetic outflow prevails. On the contrary, decreased sympathetic activity or increased vagal outflow increase the HRV both in healthy subjects and in CAD patients (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996)

In CAD patients, elevated sympathetic activity and low vagal tone predispose to ventricular fibrillation and small artery disease. Decreased HRV contributes to the progression of atherosclerotic plaques, ¯hypertension, heart failure and AMI (Neki et al. 2004). Decreased HRV has been reported in patients with metabolic syndrome (MS) and it has been hypothesized that MS may be a negative prognostic factor for CAD, through autonomic imbalance (Liao et al. 1998).

The SNS/PS also regulates the production of cytokines, inflammatory mediators involved in both the pathogenesis of atherosclerosis and depression. The activity of SNS increases and the PS inhibits the secretion of pro-inflammatory cytokines. Thayer and Sternberg (2006) proposed a model of vagal regulation of the allostatic load, unifying the mechanisms mentioned above (glucose regulation, HPA, inflammation). According to this model, vagal activity appears to play an inhibitory function in the regulation of allostatic systems. The prefrontal cortex and amygdala are important central nervous system structures linked to the regulation of these allostatic systems via the vagus nerve.

Given that CNS regulates heart rate, it has been supposed that enhanced SNS activity and decreased PS tone may be responsible for increased morbidity and mortality rates in subjects with depression, compared with the general population. Depressed patients, both physically healthy and with CAD, exhibit elevated HR, decreased HRV and greater responsiveness to provocation tests (Nahshoni et al. 2004).

Besides HRV, other methods may be used to investigate autonomic imbalance in depressive patients. Heart rate turbulence has been defined as the initial acceleration and subsequent deceleration of sinus rhythm following a ventricular ectopic beat with a compensatory pause. HRT is vagally mediated and has been shown to be an independent, powerful predictor of mortality after myocardial infarction (Francis et al. 2005). Depressed patients with recent AMI were more likely to have abnormal HRT and worse survival than non-depressed patients (Carney et al. 2007). Norepinephrine (NE)/adrenalin excess is cardiotoxic, not only because of its arrythmogenic effect, but also because it contributes to hypertension and cardiac hypertrophy, increasing mortality in patients with chronic heart failure. Recently it has been reported that patients with melanchonic MDD had increased mean around-the-clock levels of CSF NE, plasma NE, plasma epinephrine and cortisol, and an increased reactivity of the SNS to mental stress (Gold et al. 2005). Sympathetic overdrive may therefore increase the risk of mortality in patients with chronic heart failure and coexistent melancholic MDD. According to a recent study (Otte et al. 2007), patients with chronic coronary disease carrying an s allele for the serotonin transporter gene (5-HTTLPR), which is a risk factor for depression, have a high level of perceived stress and a high level of norepinephrine secretion compared to l-allele carriers, suggesting that there is a common neurobiological substrate that predisposes to depression and to increased response to stress, both behavioural and autonomic.

ANS imbalance is also linked to other mechanisms that contribute to CAD, such as platelet activation, inflammation and lipoprotein metabolism. In flow conditions typical of atherosclerotic arteries, a sudden physiological release of NE can temporarily enhance platelet deposition on a severely damaged vessel wall, while extensive exposure leads to refractoriness (Badimon et al. 1999). An autonomic imbalance in favour of the sympathetic system may also interact with inflammatory processes, contributing to the process of atherosclerosis. A study conducted on middle-aged and elderly subjects with no apparent heart disease (Sajadieh et al. 2004) showed that increased heart rate and reduced HRV were associated with subclinical inflammation in healthy middle-aged and elderly subjects and may be related to the increased mortality that has been reported in these settings. Lipoprotein metabolism is regulated by adrenergic mechanisms. Alpha-1 receptor stimulation decreases HDL and increases LDL cholesterol and VLDL triglyceride, while beta-receptor stimulation results in a net reduction of LDL and an increase in HDL (Dzau and Sacks 1987).

A deficit of inhibitory and neuromodulatory systems as PFC, PS and 5HT in depressed patients may lead to a predominance of excitatory systems as the amygdala, HPA axis and SNS, which exert their deleterious effects on myocardial tissue and vessels, increasing the risk of adverse cardiovascular events in these patients.

HPA axis

The hypothalamic release of CRH is also regulated by many neurotransmitters as ACh, NE, GABA, 5HT. The release of norepinephrine increases CRH activity during stress and vice-versa, thorough a feed-forward neuroanatomic and functional circuit between LC-NE and PVN-CRH neurons. Thus, CRH and LE-NE systems are reciprocally and positively regulated during integrated stress responses (Kling and Perini 1989, Habib et al. 2001). The central nucleus of the amygdala and the lateral bed nucleus of the stria terminalis also release CRH. In response to stressful stimuli, CRH alters the serotoninergic regulation of GABA transmission in pyramidal neurons of prefrontal cortex (Tan et al. 2004). This neuronal pathway is involved in anxiety and depression and in the regulation of working memory. Thus, CRH may contribute to impairment in emotional and cognitive processes under stressful conditions.

In depressed patients (melancholic subtype) it has been reported that chronic hyperactivation of hypothalamic CRH neurons increases HPA activity and stress response, resulting in cortisol hypersecretion, DST non-suppression and loss of cortisol circadian rhythms (Gold et al. 1988 a, b; Gold and Chrousos 2002; De Kloet et al. 1998; Claes 2004).

On the whole, however, data on CRH and ACTH levels in depressed patients seem to contrast (Parker et al. 2003). According to some studies they are increased during depressive episodes, while others report them to be normal or hypoactive; this apparent contradiction can be solved by considering that depressive disorders are not a homogeneous disease either cross-sectionally or longitudinally. Compared to severe melancholic hypercortisolemic depressive episodes, atypical lethargic hypersomnic and hyperphagic depressive episodes can be conceptualised as a hypoactive state of the stress system that has yielded too readily to counter-regulatory restraints (Gold and Chrousos 2002). Longitudinally, episodes have to be considered as dynamic processes; while for example, in acute depression, the hypersecretion of CRF stimulates ACTH which, in turn, stimulates cortisol synthesis and secretion, in chronic depression cortisol levels remain elevated while ACTH levels are reduced, due to the increased response of the adrenal cortex to ACTH and the negative feed-back of glucocorticoids on the pituitary gland. Lastly, it has been reported that decreased cortisol plasmatic levels can be found in the long term, probably as a result of exhaustion/depletion (Carroll et al. 2007).

Glucocorticoids

In patients with MDD, HPA axis dysfunction precedes the onset of symptoms. HPA dysfunction has been reported with increased plasma and urinary levels of glucocorticoids (GC) and DST non-suppression in between 40 and 60% of severely depressed patients (Arana et al. 1985, Gold and Chrousos 2002, Carroll et al. 2007). The proportion of hypercortisolemic patients increases with age and number of lifetime episodes (Lenox et al. 1985). The HPA often returns to normal activity as depressive symptoms resolve, but persistent dysregulation is a risk factor for non-response or relapse in MDD (Arana et al. 1985). Healthy subjects at high familial risk for affective disorders also have dysregulated HPA, confirming the hypothesis that hereditable factors could lead to alterations in HPA axis responsiveness that conducive to depression (Ising et al. 2005). Due to the high proportion of depressed patients with a dysregulated, hyperactive HPA, glucocorticoid excess may be one of the principal links between central mood disease and CAD. In extreme cases, depressed hypercortisolemic patients exhibit the clinical features of Cushing's Disease, called pseudo-CD (Chrousos 2000), and are at high risk of developing metabolic changes (insulin resistance, increased visceral fat) and atherosclerosis, similarly to patients with CD. During stress response, hypercortisolism contributes to the pathogenesis of hypertension, together with catecholamine, vasopressin, endorphins and aldosterone (Zimmerman and Frohlich 1990). A recent study on the direct effects of natural and synthetic GC on tPCK expression in coronary arteries demonstrates that GC are potent stimulators of specific PKC isoform expression and subcellular distribution in coronary smooth muscle cells (Maddali et al. 2005). Thus GC may cause hypersensitivity of microvessels' vascular smooth muscle cells (VSMC) to vasopressor substances and increase VSMC growth, proliferation and contraction through the activation of specific PCK, leading to the development of hypertension and atherosclerosis. Hypercortisolism may also activate the endothelial system, as demonstrated in a study on CD (Kirilov et al. 2003).

Major depressive disorder has been associated with decreased responsiveness to glucocorticoids (glucocorticoid resistance), which is believed to be related in part to impaired functioning of the glucocorticoid receptor (GR). Glucocorticoid resistance, in turn, may contribute to excessive inflammation as well as hyperactivity of CRH and SNS that contribute to a variety of diseases as well as behavioral alterations. Recent data indicate that GC resistance may be a result of impaired GR function secondary to chronic exposure to inflammatory cytokines as may occur during chronic medical illness or chronic stress (Pace et al. 2007).

Metabolic syndrome

The metabolic syndrome (MS), also known as Syndrome X or the insulin resistance syndrome, is a set of commonly co-occurring conditions that include obesity (particularly abdominal obesity), insulin resistance, impaired glucose tolerance, disturbances in uric acid and lipid metabolism, hypertension and prothrombotic and proinflammatory states, which all increase the risk of cardiovascular disease.

The relationship between MS, CAD and depression is an object of interest and concern, considering that 20-25% of adults in the US population suffer from MS (Ford et al. 2002). Since MS is an important risk factor for the development of CAD, the prevalence of depression in subjects with MS is about four times higher than in subjects without depression.

Depressed patients with MS also exhibit higher SNS activity (Petrlova et al. 2004). A nested case-control study (Brunner et al. 2002) measured adrenocortical, autonomic and inflammatory parameters in patients with MS and in matched healthy controls. Patients with MS exhibited functional alteration of both major neuroendocrine stress pathways. Interestingly, the link between psychosocial exposure, MS and autonomic and sympathoadrenal activity was more consistent than that with HPA activity. It has been hypothesized that enhanced sympathetic and decreased adrenal medullary activity link insulin resistance, hypertension and metabolic abnormalities. Moreover, insulin resistance seems to alter sympathetic activity. In healthy subjects there is an inhibitory pathway between the ventromedial hypothalamus and sympathetic centres in the brain stem, which is activated by decreased glucose metabolism during fasting and decreases central sympathetic activity. In insulin-resistance, as in the postprandial state, high insulin plasma levels stimulate glucose metabolism by hypothalamic cells, impairing the activity of the inhibitory pathway and increasing central sympathetic activity (Reaven et al. 1996). Subsequently, both hyperinsulinemia and autonomic imbalance lead to hypertension, increased triglycerides and decreased HDL cholesterol, i.e. to the development of the classic risk factors for atherosclerosis.

A possible synergistic effect of obesity and depressive mood on chronic low level inflammation could play a crucial role in the pathogenesis of atherosclerosis. Some authors found depressive mood to be significantly associated with C-reactive protein (CRP) in obese but not in non-obese men. Higher CRP levels in clinically depressed individuals are positively associated with body mass index (Ladwig et al. 2003).

Platelet dysfunction

Since the pioneeristic hypothesis by Markovitz and Matthews (1991), many studies have shown that enhanced platelet responses to psychological stress might promote adverse coronary ischemic events. Platelet activation contributes to the progression of acute coronary syndrome (Hamm 1987). Depressed patients exhibit enhanced platelet aggregation, at baseline and after orthostatic challenge (Musselmann 1996), as assessed by increased plasma PF4 and âTG and greater concentrations of intracellular calcium after stimulation with 5HT (Schins et al. 2003, 2004).

The exact mechanism that links platelet dysfunction and depression is not yet completely understood. Serotonin plays a pivotal role both centrally in the pathophysiology of depression, and peripherally in promoting thrombogenesis: serotonin binds 5HT transporter and 5-HT_{2A} receptors both in the CNS and in platelets. Central 5-HT_{2A} receptors up-regulation in depression suggests a functional deficit of pre-synaptic serotonin, which is considered a basic mechanism for mood dysregulation; peripherally depressed patients show signs of a hyperactive platelet 5-HT_{2A} receptor signal transduction, which promotes calcium mobilisation, platelet aggregation and vasoconstriction (Shins 2003). Depressed post-MI patients show increased 5-HT_{2A} receptor binding compared to non-depressed post-MI patients (Shins 2005a). Serotonin seems to play a central role not only in the pathophysiology of depression, but also in promoting thrombogenesis: 5 HT promotes platelet aggregation and vasoconstriction through 5-HT_{2A} receptors. Although 5HT is a weak platelet agonist, it amplifies the action of other promoting substances as ADT, TXA2, thrombin and catecholamines. It has been shown that an excessive transcardiac accumulation of 5HT makes chronic stable angina worse, leading to instable coronary syndrome. (Willerson et al. 1991).

The only mechanism that allows the uptake of 5HT inside the platelets is the 5HT transporter. This transporter presents a polymorphism (5-HTTLPR) that is linked with increased 5HT uptake and with a greater risk of AMI (Schins et al. 2005a, 2005b). Among patients with chronic coronary illness, carriers of the s allele of 5-HTTLPR are more vulnerable to depression, perceived stress, and high norepinephrine secretion. These factors may contribute to the worsening of cardiovascular outcomes in these patients (Otte 2007). Variation of 5HT transporter gene influences the activity of the HPA axis and stress response in infant rhesus macaques (Barr et al. 2004). Cortisol might enhance the uptake of 5HT by raising the synthesis of 5HT transporter, causing a reduction in the level of the neurotransmitter in the synaptic cleft (Tafet 2001a, 2001b).

Although many biochemical mechanisms are clarified, the right causative link between depression, platelets and heart is still the object of discussion. According to the "platelet hypothesis," patients with depression present abnormalities. Serotonin metabolism is abnormal in depressed patients' brains as well as in their platelets. These platelet abnormalities may predispose CAD patients with depression to having platelets more likely to degranulate to certain triggers, leading to thrombosis that can cause an acute MI or unstable angina. Platelets are a critical component in the pathophysiology of CAD, and platelet abnormalities can therefore exacerbate the development and progression of CAD (Somberg and -Arora 2008)

Endothelial dysfunction, depression and CAD

Recent evidence suggests that depressive disorders are associated with vascular endothelial dysfunction. MDD is associated with striking abnormalities of endothelial function and elevation of circulating markers of atherosclerosis propensity in patients with or without traditional coronary risk factors (Rajagopalan et al. 2001, Pizzi et al. 2008).

Depressive disorders are also associated with endothelial dysfunction in patients with CAD (Sherwood 2005).

Many mechanisms have been discussed regarding the role of depression on endothelial wall. A recent article found evidence of decreased numbers of circulating endothelial progenitor cells (EPCs) in patients with a current episode of major depression (Dome et al. 2008).

Recent studies advocate that the L-arginine-nitric oxide (NO) pathway is involved in the genesis of depression. NO contributes to endothelial functions

including neurotransmission and platelet aggregation inhibition. A recent review stressed that in depressive patients, the L-arginine-nitric oxide pathway seems to be impaired (Pinto et al. 2008).

Cytokines, inflammation, depression and CAD

Inflammatory cytokines induce important changes in the vessel wall including reduction of the bioavailability of endothelial nitric oxide synthase and nitric oxide synthesis (Verma et al. 2002). Decreased nitric oxide activity contributes to modifying endothelial function causing impairment of endothelial-dependent vasodilatation (Joannides et al. 1995).

Growing evidence suggests that arteriosclerosis can be considered a systemic inflammatory disease (Brueckmann et al. 2004). In MDD, too, there is evidence of increased systemic inflammation (Maes 1999, Appels et al. 2000, Raison et al. 2006), which in turn may increase the risk of CAD (Miller et al. 1999, Lesperance et al. 2004). Patients with MDD do in fact have activated inflammatory pathways, as shown by increased levels of pro-inflammatory cytokines, increased acute-phase proteins (APP), chemokines and adhesion molecules (Maes et al. 1999). Cytokines may act as central neuromodulators in cognitive and neuroendocrine pathways, leading to prolonged central HPA activity, reduced brain serotonin functioning, neurodegeneration, reduced neuroprotection and reduced hippocampal neurogenesis, in a neuroimmune cytokine hypothesis of depression (Schiepers et al. 2005).

The pathogenetic role of inflammation is better delineated in atherosclerosis and CAD than in mood diseases (Napoleao 2007). Inflammation is also involved in the most dramatic consequence of atherosclerosis: acute myocardial infarction (for a recent review about inflammation in AMI see Alber et al. 2005 and Skala 2006). Inflammatory markers are increased in patients with acute coronary syndrome, remain elevated during long-term follow-up and predict outcome of CAD, supporting the concept that systemic rather than local vascular inflammation contribute to the development of atherosclerosis (Brueckmann et al. 2004, Murtagh and Anderson 2004). Sudden CAD progression leading to AMI seems to be triggered/ accompanied by prolonged immune activation (Mizia-Stec et al. 2003) that also mediates reperfusion injury after AMI and is a strong predictor of the risk of serious coronary events in patients with unstable angina pectoris (Koukkunen et al. 2001). Moreover, cytokines may contribute to the onset of high blood pressure.

More complex is the link between depression and inflammation (for a recent review see Schiepers et al. 2005). Primary depression has recently been linked by several groups of researchers to a state of low grade chronic inflammation, with an increase in pro-inflammatory cytokines (IL-1,IL-2, ,IL-6, TNF alpha and IFN), as a result of *in-vivo* systemic activation of cell-mediated immune responses, which can also persist in the remitted state (Maes 1999, Raison et al. 2006, Kling et al. 2007). These cytokines have a complex cascade of central effects, including strong activation of the HPA axis with increased level of GC, causing neurotoxic damage of the hippocampus and other brain regions rich in GC receptors, as the anterior cingulated cortex (ACC). Besides the HPA axis, several other CNS pathways may interact with the immune system. Cytokines in particular may modulate central monoamine activity and induce alterations in neuroplasticity (Lacosta et al. 2000, Hayley et al. 2005). A major neurodegenerative pathway linked to the increased activity of cytokines in the brain has been identified, as the result of increased endogenous neurotoxins as end products of the tryptophan-kynurenine pathway (Moroni 1999, Wichers and Maes 2004). Pro-inflammatory cytokines stimulate TDO/IDO catabolic enzymes, leading to an increase in neurotoxin 3-hydroxykynurenine (3-OHK) and quinolinic acid (QA) - produced in the brain by activated microglia - and to a reduction in serotonin synthesis. QA has neurotoxic activity mainly through the agonism of N-methyl d-aspartate (NMDA) receptors. Kynurenic acid (KA), produced by astrocytes, has neuroprotective properties. Further damage of astrocytes by QA progressively increases the chronic imbalance between the two cellular components and the two pathways. It is likely, but yet to be fully explored, that low grade inflammation may add to the other stress-related neurotoxic pathways in recurrent mood disorders, both primary or secondary, in causing not only increased neuronal loss by apoptosis, but also impaired constitutive neurogenesis in the mood-relevant network of hippocampal formation (DG).

Given that inflammation takes part in the pathogenesis of both CAD and MDD, there are many different levels of interaction to explain the link between immune system activation and the two diseases. Inflammation could be a common mechanism in the pathogenesis of CAD and MDD or it may accompany one and take part in onset of the other (Rimar and Rimar 2004). Activation of the immune system results not only in sickness behavior but also in the occurrence of neurovegetative symptoms and psychological signs of depression. In turn, these mental alterations impact on the immune system and result in a shift toward TH1 immunity, which further increases inflammation, heightening the risk of both CAD and depression (Dantzer 2008). This may explain the complex relationship existing between these two relapsing /evolving and often chronic diseases.

Although many studies have investigated the link between depression, inflammation and CAD, the results are not always concordant. A recent study did not find any indication of increased inflammation in depressed post-AMI patients as compared to controls (Schins et al. 2005a). Depressed patients exhibited greater adiposity than controls which after adjusting for body mass, seemed to be responsible for the elevated levels of inflammatory markers.

An important factor in the relationship between inflammation, CAD and depression is time and evolution in distinct phases. Gidron et al. (2002) reviewed the psychoneuroimmunogic three-stage immunobiological model of acute coronary syndrome, introducing psychosocial factors. The three stages of acute coronary syndrome are plaque instability, plaque rupture and thrombosis. Proinflammatory cytokines and leukocytes play a key role in plaque instability and are

related to acute stress, hostility, depression and vital exhaustion. Plaque rupture is also promoted by catecholamines which induce vasoconstriction and elevated blood pressure and are linked to acute stress and hostility/anger. Finally, platelet aggregation contributes to thrombosis and is correlated to depression, hostility and vital exhaustion. Kop (2003) proposed a selective review of the interplay between psychological factors and immunological processes related to the different stages of CAD. He enucleated three types of psychological risk factors related to the three stages of CAD: chronic, episodic and acute. Chronic psychological risk factors, as hostility and low socioeconomic status, contribute to the early stage of disease and episodic factors (depression, exhaustion) to plaque instability; acute triggers, as mental stress and anger, promote myocardial ischemia and plaque rupture.

Conclusons

Given the complexity of MDD and CAD pathophysiology and the number of brain structures involved in mood and cardiovascular regulation, it seems simplistic and not supported by data to consider one hypothesis to be superior to the others. The HPA-axis, ANS, platelets and inflammation cascade are tightly bound in a close network of complex interrelated links, all of which have to be considered in the pathophysiology of MDD-CAD comorbidity.

Neurotransmitters, hormones and cytokines are the major biological effectors in central and peripheral response to stress. Peripheral effectors of stress response, such as cortisol, norepinephrine and adrenaline, are secreted under central control, with the contribution of limbic structures and the prefrontal cortex, which are involved in the pathogenesis of depressive symptoms. Chronic and profound alterations, both genetic and acquired, to stress response system regulation (allostatic load) are to be considered at the basis of both MDD and cardiovascual disorders (McEwen 2008).

Central alterations in the stress-integrated system (PFC, amygdala, hippocampus, paraventricular nucleus of the hypothalamic, LC-Ne) and serotoninergic tone could represent a link between MDD and CAD, by inducing dysregulation of the peripheral balance of the effectors:

- Glucocorticoid excess with deleterious effects on both the cardiovascular system (contributing to MS and atherosclerosis and potentiating other cardiotoxic substances, as catecholamines) and SNC, being neurotoxic for mood-relevant brain structures.
- ANS imbalance with SNS prevailing on PS, with adverse effects on the electrical and contractile activity of the myocardium.
- Increased cytokine production in a low-grade inflammation state, which may participate in MDD by interfering with central serotoninergic activity and neuroplasticity,- and is responsible for atherosclerosis onset and development of CAD
- Enhanced platelet reactivity, both in MDD and in CAD, which is a peripheral marker of abnormal serotonin regulation in MDD and contributes to progression of CAD

Future studies on genetic and brain imaging correlates of this complex comorbidity, together with a refinement of diagnostic, treatment and preventive tools, will help in managing and reducing the risk of these two common, highly disabling conditions.

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