Neuroinflammation at the interface of depression and cardiovascular disease: Evidence from rodent models of social stress

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A B S T R A C T

A large body of evidence has emerged linking stressful experiences, particularly from one’s social environment, with psychiatric disorders. However, vast individual differences emerge in susceptibility to developing stress-related pathology which may be due to distinct differences in the inflammatory response to social stress. Furthermore, depression is an independent risk factor for cardiovascular disease, another inflammatory-related disease, and results in increased mortality in depressed patients. This review is focused on discussing evidence for stress exposure resulting in persistent or sensitized inflammation in one individual while this response is lacking in others. Particular focus will be directed towards reviewing the literature underlying the impact that neuroinflammation has on neurotransmitters and neuropeptides that could be involved in the pathogenesis of comorbid depression and cardiovascular disease. Finally, the theme throughout the review will be to explore the notion that stress-induced inflammation is a key player in the high rate of comorbidity between psychosocial disorders and cardiovascular disease.

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List of abbreviations: 5-HT, Serotonin; BDNF, Brain-derived neurotrophic factor; CRP, C reactive protein; CVD, Cardiovascular disease; CRF, Corticotropin-releasing factor; DA, Dopamine; DR, Dorsal raphe; INF, Interferon; IL, Interleukin; IL-1Ra, Interleukin 1 receptor antagonist; IL-1r2, Interleukin 1 receptor type 2; KYN, Kynurenine; LPS, Lipopolysaccharide; LC, Locus coeruleus; MCP, Monocyte chemotactic protein; NPY, Neuropeptide Y; NE, Norepinephrine; PTSD, Post traumatic stress disorder; SSRI, Selective serotonin re-uptake inhibitor; TNF, Tumor necrosis factor; Trk, Tyrosine receptor kinase.

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1. Introduction

Depression is one of the most common psychosocial disorders in the United States, affecting nearly 7% of adults and more than 10% of adolescents (National Institute of Mental Health, 2013a,b). Approximately 10–30% of those suffering from depression exhibit treatment resistance (Al-Harbi, 2012), which has been linked to an increase in circulating cytokines (Maes et al., 1997; Musselman et al., 2001b; Miller et al., 2002; Alesci et al., 2005; Motivala et al., 2005; Raison et al., 2013). Although much of what is known about inflammation and depression has been determined by studying cytokine levels in the plasma, elevated pro-inflammatory cytokines are also reported in the cerebrospinal fluid (CSF) of subpopulations of depressed patients (Sasayama et al., 2013; Kern et al., 2014; Devorak et al., 2015). It has only recently been shown for the first time using positron emission tomography that microglial activation is increased in the brains of depressed patients compared to healthy controls, and was positively correlated with severity of depressive symptoms (Setiawan et al., 2015). Together these data indicate that the alterations in inflammatory markers exhibited by a subset of depressed patients represent a complex dysfunction of the immune system incorporating both the brain and the body. Furthermore, suffering from depression greatly increases the risk of developing other inflammatory-related medical disorders such cardiovascular disease (CVD), which may be precipitated by the same systems involved in depression (Seligman and Nemeroff, 2015). A major focus of this review is to elucidate the impact that neuroinflammation can have on neurotransmitters and neuropeptides within the brain that are linked to depression and exhibit neurogenic control of cardiovascular function, thereby providing a window into how inflammation within the brain could not only contribute to psychiatric illness, but also increase risk for CVD.

2. Social stress and coping in humans

Social stress such as bullying, abuse, or taking care of a terminally ill loved one is the most common type of stress individuals will face in their lifetime (Almeida, 2005) and personal perception of a social stressor is predictive of whether one will develop depressive symptoms (Nicolai et al., 2013). Additionally, patients suffering a depressive episode or in remission from depression exhibit increased sensitivity to social stressors encountered in daily life, indicating the robust nature of this stressor (van Winkel et al., 2015). Social stress and depression can affect anyone regardless of age, gender, ethnicity, or socio-economic background; however only a portion of the population is susceptible. The phenomenon by which stress exposure leads to psychosocial disorders in one individual while another remains resilient is well recognized, however, the mechanisms driving these individual differences are not well understood. One factor related to susceptibility and resiliency is the individual coping style adopted to deal with the stressor. In both animals and humans it has long been suggested that two diverse coping responses to social stress can be distinguished (Henry and Stephens, 1977). Active coping, originally described by Walter Cannon (Cannon, 1915) is characterized as the fight or flight response, while passive coping is characterized by low levels of aggression and heightened immobility (Engel and Schmale, 1972). In humans, the use of passive coping strategies, such as avoidance, withdrawal, and seeking excessive reassurance/negative feedback, has been correlated to a greater susceptibility of developing depression (Cambron et al., 2009; Cairns et al., 2014); while active coping, such as problem solving, seeking support, and engaging in adaptive processes has been related to resiliency (Cairns et al., 2014). In addition, it has been shown that patients who more readily adopt passive coping strategies are not only more susceptible to developing depression, but also exhibit greater lipopolysaccharide (LPS) stimulated IL-6 release from whole blood samples as compared to patients who more commonly adopt active coping strategies (Bouhuys et al., 2004). Thus since different coping strategies result in unique inflammatory responses, coping may be related to the physiological consequences associated with stress exposure and may contribute to comorbid medical disorders such as CVD.

The impetus for this review is to investigate evidence of inflammatory responses that are tightly coupled to individual differences in stress susceptibility. Particular focus will be directed towards reviewing the literature underlying the impact that stress-related neuroinflammation has on neurotransmitters and neuropeptides that could be involved in the pathogenesis of comorbid depression and cardiovascular disease. Given the clinical relevance of studying the inflammatory response under conditions of social stress, our literature review focused mainly on studies utilizing modified resident-intruder models of social defeat stress. It is important to note that the visible burrow system is another highly relevant social stress model that provides significant insight into social stress (Blanchard and Blanchard, 1989; Blanchard et al., 1995; McEwen et al., 2015); however, due to the lack of studies investigating inflammation with this model, it does not fall within the scope of this review.

3. Modeling social stress and coping in rodents using repeated social defeat stress

The resident-intruder paradigm, originally developed by Miczek (Miczek, 1979), takes advantage of the social hierarchy and the continuing struggle for male dominance intrinsic to rodents (rats, mice, prairie voles) in order to model the effects of social stress (Buwalda et al., 1999; Bhatnagar and Vining, 2003; Berton et al., 2006; Trainor et al., 2010, 2011; Wood et al., 2010; Trainor et al., 2011). Social stress, however, is not limited to rodents and has been demonstrated in tree shrews and other non-human primates (Shively and Willard, 2012). Since one of the first descriptions of the resident-intruder model of social stress (Miczek, 1979), many
laboratories run a modification of this repeated social defeat test which often involves placing a male “intruder” into the home cage of an unfamiliar more aggressive male “resident” for 5–60 min (Sgoifo et al., 1996; Buwalda et al., 1999; Bhatnagar and Vining, 2003; Berton et al., 2006; Krishnan et al., 2007; Wood et al., 2010; De Miguel et al., 2011; Gomez-Lazaro et al., 2011). These models of repeated exposure to acute (minutes to hours) social stress have consistently been shown to result in robust activation of the sympathetic nervous system, increased susceptibility to arrhythmia, elevated blood pressure, increased activation of the hypothalamic-pituitary-adrenal axis, and have been shown to disrupt a variety of other physiological endpoints which are relevant in the study of human pathology (Tornatzky and Miczek, 1993, 1994; Sgoifo et al., 1996; Bhatnagar et al., 2006; Wood et al., 2010, 2012; Carnevali et al., 2013; Sgoifo et al., 2014).

Similar to humans, stress exposure has been shown to result in ethologically relevant passive and active coping behaviors in fish, rodents, pigs, and non-human primates (Koolhaas et al., 1999, 2007; Silh et al., 2004; Bell, 2007; Koolhaas et al., 2007; Reale et al., 2007). We and others have demonstrated the utility of the resident-intruder paradigm to study the differential consequences associated with the emergence of active and passive coping responses in the context of repeated social defeat exposure (Korte et al., 1992; Fokkema et al., 1995; Gomez-Lazaro et al., 2011; Wood et al., 2012; Chajale et al., 2013; Perez-Tejada et al., 2013; Reyes et al., 2015; Wood et al., 2015). Analysis of behavior exhibited during defeat, such as immobility and exploration (De Miguel et al., 2011; Gomez-Lazaro et al., 2011; Perez-Tejada et al., 2013) or duration of upright posture and the latency to exhibit a supine posture signaling defeat (Wood et al., 2012, 2015; Reyes et al., 2015; Wood et al., 2015) can be used to statistically separate animals into passive or active subpopulations. Specifically, passive coping rodents are characterized by high levels of immobility, reduced exploratory behavior, little time spent in upright postures, and a short latency to display supine postures in response to an attack by the resident (De Miguel et al., 2011; Gomez-Lazaro et al., 2011; Wood et al., 2012; Perez-Tejada et al., 2013; Reyes et al., 2015; Wood et al., 2015), which is associated with the development of depressive-like behavioral endpoints as evidenced by increased immobility in the forced swim test (Wood et al., 2010; Gomez-Lazaro et al., 2011; Perez-Tejada et al., 2013) and reductions in sucrose preference (Wood et al., 2015). In addition, passive coping rodents generally display low plasma norepinephrine (NE) (Korte et al., 1992; Perez-Tejada et al., 2013) and high plasma corticosterone concentrations during stress (Wood et al., 2010; De Miguel et al., 2011; Gomez-Lazaro et al., 2011). In contrast, active coping rodents spent more time attacking/threatening the resident, spend greater time in upright postures and generally resist defeat. Interestingly, active coping rats do not exhibit the same behavioral deficits evident in passive coping rats and tend to show lower plasma corticosterone, increased noradrenergic responsivity during stress, and greater sympathetic activity in response to social defeat as compared to their passive counterparts (Fokkema et al., 1995; Wood et al., 2010; De Miguel et al., 2011; Gomez-Lazaro et al., 2011; Perez-Tejada et al., 2013). Even though the differential consequences to stress exposure based on coping have been well established in rodents and parallels what is seen in humans, the neurobiological mechanisms driving these differences are not well understood.

In addition to assessing the coping response, many labs measure individual differences based on other social behaviors or behavioral responses to a subsequent stressor. For example, categorizing rats based on dominant versus submissive pairs assesses the different behavioral responses between conspecífics as they establish a dominant or submissive relationship during the defeat exposure. Dominants or winners are generally more resilient to the consequences of social defeat and exhibit greater aggressive behavior during the defeat exposure (Morrison et al., 2014; Stewart et al., 2015). Other groups categorize mice as susceptible or non-susceptible based on changes in social interaction following repeated social defeat exposure (Krishnan et al., 2007; Hodes et al., 2014). Unlike other methods for determining individual differences, the high/low responder method exposes animals to a novel environment prior to stress exposure and animals deemed as high responders exhibit greater locomotion in the novel environment compared to low responders (Calvo et al., 2011; Ducloy et al., 2011; Hollis et al., 2011; Kumar et al., 2014). In general, low responders exhibit a greater resilience to the consequences of social stress as measured by the open field, social interaction, and sucrose preference tests (Calvo et al., 2011; Ducloy et al., 2011; Hollis et al., 2011; Kumar et al., 2014). However, opposing data also suggests that high responders that exhibited greater active coping during defeat could be more susceptible to developing depressive-like behavior (Calvo et al., 2011). Although the methods of determining individual differences varies and each has inherent advantages and disadvantages, they all provide valuable insight into the dichotomy which exist in susceptibility to social stress and parallel many of the differences seen in the human population.

### 3.1. Modeling gender differences in social stress

There is a growing body of evidence on health disparities between women and men, with women being strikingly more susceptible to developing stress-related psychosocial disorders including depression (Hankin et al., 1998), anxiety (Lewinsohn et al., 1998), and post-traumatic stress disorder (Breslau, 2002). Women have been shown to be more sensitive to stress with regard to housing problems, loss of a confidant, and marital stress (Kendler et al., 2001; Derry et al., 2013) and are more likely to suffer consequences from childhood bullying (Takizawa et al., 2015). Interestingly, acute injection with endotoxin has shown that women are also more susceptible to inflammatory-induced depressive behavior (Moieni et al., 2015). Animal studies investigating the effect of social stress in females are severely lacking due to the challenge of running social defeat stress in a female population. In rats, males residents will not attack females; therefore, modified female social defeat models have been established using highly territorial Syrian hamsters (Huhman et al., 2003) or highly aggressive lactating female rats (Ver Hoeve et al., 2013; Shimamoto et al., 2015). In these studies it is unclear whether female “intruder” rats are more sensitive to social defeat stress than male “intruders”. In fact, Haller and colleagues directly compared the effect of social defeat stress in males versus females on stress relevant endpoints (weight gain, adrenal weight, plasma corticosterone) and revealed that males were more sensitive to social defeat (Haller et al., 1999). California mice also represent a useful species to study gender differences in susceptibility to social defeat as females develop greater social avoidance behavior and demonstrate marked changes in central stress-sensitive molecules such brain derived neurotrophic factor (BDNF) in response to social defeat exposure as compared to males (Trainor et al., 2010, 2011; Greenberg et al., 2014, Greenberg et al., 2015).

While studying social defeat in female rats is inherently challenging and may not have the same impact or intensity as in males, other types of social stress may be better suited to study stress susceptibility in females. For example, females have been reported to be more sensitive to social instability stress than their male counterparts (Haller et al., 1999). Furthermore, another body of literature involving social isolation in prairie voles, a highly social and monogamous rodent, has indicated that social isolation
produces depressive-like behaviors in females as well as robust changes in cardiovascular function (Grippo et al., 2007, 2008). Interestingly, the behavioral and cardiovascular changes that occur following social isolation in female prairie voles are comparable to those observed following social defeat in males (Sgoifo et al., 2001; Wood et al., 2012, 2015). Importantly, the impact of social stress in females on inflammatory measures is greatly needed.

4. Individual differences in social stress-induced inflammation in the periphery

Social stress in humans within a laboratory setting, as modeled by the Trier social stress test, has shown that enhanced feelings of anxiety and depression are correlated with increases in stress-induced inflammation in plasma (Carroll et al., 2011; Christian et al., 2013). In animal studies social stress-induced inflammation has been well characterized. Without taking individual differences into account, social stress has been shown to increase the number of macrophages and stimulate the expression of cytokine mRNA and the release of IL-6 and TNF-α in the plasma (Wohleb et al., 2012, 2014b; Powell et al., 2013; Wohleb et al., 2014b). Furthermore, individual differences studies reveal that stress susceptible rats and mice exhibit increases in pro-inflammatory cytokines such as IL-6, IL-15, IL-7, monocyte chemotactic protein (MCP)-1, and IL-1β (Hodes et al., 2014; Stewart et al., 2015; Wood et al., 2015). In contrast, stress resilient rats or mice do not exhibit elevations in proinflammatory cytokine expression in the plasma, but do exhibit greater expression of anti-inflammatory IL-4 and IL-10 (Hodes et al., 2014; Stewart et al., 2015). It is important to note that determination of stress-induced inflammation in the plasma is largely dependent on collection time. A study by Hodes et al. (2014) illustrated that IL-6 was significantly elevated 20 min after the first social defeat exposure in their susceptible population of mice and although IL-6 was again elevated above controls when analyzed 48 h after the 10th and final stress exposure, the concentration had dropped by nearly 50%. Alternatively social defeat studies in rats identified that defeat-induced IL-6 levels were elevated in susceptible, passive coping rats just one hour after the 5th stress exposure and returned to normal within 24 h (Wood et al., 2015). Furthermore, changes in MCP-1 levels, a pro-inflammatory chemokine responsible for inflammatory cell recruitment, were unremarkable just one hour after the 5th and final defeat exposure, yet were significantly elevated 24 h after the 5th social defeat exposure (Wood et al., 2015). These data indicate that although stress induces inflammation in the periphery, this response may be transient, rely heavily on collection time, and differs based on individual cytokines.

In addition to bone marrow, the spleen also functions as a reservoir for monocytes to be released into the blood stream. Therefore, splenic release of inflammatory cytokines may provide insight into the long lasting peripheral changes that occur in response to social stress. In many cases social stress has been shown to cause an increase in splenic weight termed splenomegaly (Kinsey et al., 2008; Wohleb et al., 2012, 2014b; Goto et al., 2015), which is accompanied by increases in the number of monocytes within the spleen and greater release of pro-inflammatory cytokines such as IL-6 and TNF-α (Kinsey et al., 2008). While data assessing individual differences in splenic inflammation in response to social-stress is largely uncharacterized, findings by Gomez-Lazar et al. (2011) demonstrated that susceptible mice generally exhibit increased splenic release of pro-inflammatory cytokines (IL-6, TNF-α) when stimulated with the T-cell stimulating agent concanavalin A. Our lab has recently confirmed these findings using repeated social stress in rats (Finnell et al., unpublished). In contrast, a study conducted by De Miguel et al. (2011) demonstrated that resilient rats exhibited greater splenic release of IL-1β and IL-2 as compared to passive and control counterparts. These conflicting accounts of inflammatory responses in susceptible and resilient rats may arise from differences in the schedule and duration of stress exposure. Based on these studies, resilient animals demonstrated a greater splenic response to acute social stress exposure (De Miguel et al., 2011), while the maladaptive spleenomegaly and persistent cytokine release evident in susceptible animals may develop in response to repeated social defeat exposure (Gomez-Lazar et al., 2011). Together these data demonstrate the complex nature inherent in social stress-induced alterations in peripheral inflammation and indicate the need for further research specifically in the context of individual differences.

5. Individual differences in social stress-induced neuroinflammation

As described in the introduction, there is considerable evidence to suggest that elevated neuroinflammation occurs in subsets of depressed patients and may be correlated to symptom severity (Sasayama et al., 2013; Kern et al., 2014; Devorak et al., 2015; Setiawan et al., 2015). Animal studies of social defeat stress corroborate these findings by revealing that social stress exposure leads to long lasting increases in not only the number of macrophages and activated microglia in the brain (Stankiewicz et al., 2015), but also exaggerated activation of these cell types, promoting increased expression of pro-inflammatory cytokines such as IL-1β and TNF-α (Wohleb et al., 2011, 2012, 2014a). Microglia and macrophages play a large role in the inflammatory response to social defeat, yet the important distinction as to whether social stress promotes M1 (pro-inflammatory) or M2 (anti-inflammatory) microglial polarization has yet to be identified (Franco and Fernandez-Suarez, 2015). In general, social defeat has been shown to promote a pro-inflammatory phenotype within the brain by increasing the expression of cytokines such as IL-1β, IL-6, and TNFα in critical brain regions associated with depression (Audet et al., 2011; Patki et al., 2013), which are generally secreted in high concentrations from M1 type microglia (Franco and Fernandez-Suarez, 2015). Importantly, several endogenous molecules such as cannabinoids, steroid hormones, substance P, and glucocorticoids have been shown to promote M2 over M1 microglial activation. (Franco and Fernandez-Suarez, 2015). Therefore, understanding the balance between these activated states in response to stress could provide valuable insight into not only the adaptive/maladaptive role of microglia in the central nervous system, but also alternative treatment methods for diseases associated with high levels of inflammation.

Individual differences in stress susceptibility are also evident at the level of neuroinflammation. Rats characterized as susceptible generally exhibit greater release of IL-1β within the locus coeruleus (LC) (Wood et al., 2015), the major noradrenergic nucleus within the brain that has been associated with depression (Ressler and Nemeroff, 2000; Serafini, 2012). These alterations in neuroinflammation are region specific, as this effect is not exhibited uniformly throughout the brain. In fact, within the dorsal raphe (DR), a major serotonergic center of the brain, IL-1β was not elevated in susceptible rodents; however resilient rats exhibited an adaptive decrease of IL-1β in the DR (Wood et al., 2015). Furthermore, elevated cytokines are not specific to susceptible rats; significantly elevated IL-1β mRNA was reported in the hypothalamus of resilient mice after two stress exposures over a 12 day period (De Miguel et al., 2011). While these data seem contradictory, social stress produces region specific alterations in activity that is also contingent upon duration of stress exposure (Morrison et al., 2014). We have previously demonstrated that susceptible and
resilient rats exhibit complex differential regulation of gene expression within both the LC and the DR relative to control rats. In the LC, where susceptible rats exhibited greater IL-1β mRNA levels and resilient rats exhibited decreased IL-1β and TNF, social defeat altered the expression of several other genes, many of which have a role in immune or inflammatory processes. For example, genes encoding for receptors of interleukin, beta-adrenergics, and neutrophil Y, as well as cytochrome P450s, Matrix metalloproteinases, and cellular adhesion molecules were altered by defeat, and in many cases were unique to susceptible rats. In contrast, within the DR, there were nearly 2.5 times more genes affected by stress in susceptible rats than in their resilient counterparts (Wood et al., 2015). Similar to that found in the LC, there were several inflammatory-related genes that were altered by stress exposure. Of considerable interest, inducible nitric oxide synthase, a signaling molecule involved in the pathogenesis of inflammatory disorders was reduced by more than 6 fold in resilient rats (vs. controls) while susceptible rats demonstrated a modest 1.8 fold reduction. This drastic decrease in iNOS in resilient rats may represent a protective mechanism recruited during active coping (Wong et al., 1996) as iNOS suppression has been shown to promote M2 (anti-inflammatory) type microglia (Franco and Fernandez-Redon, 2015). While significant differences in gene expression patterns exist when comparing resilient and susceptible populations, it is important to note that there are also some commonalities between these groups as seemingly protective effects of changes in gene expression also emerged. For example, increased expression of the IL-1 receptor type 2 (IL-1r2) a decoy receptor was evident in the LC (McMahan et al., 1991; Wood et al., 2015) and increased expression of suppressor of cytokine signaling 3 in the ventral tegmental area was identified in both susceptible and resilient groups (Krishnan et al., 2007).

It is important to note that repeated exposure to social stress may be required for these robust alterations in neuroinflammation. Hueston and colleagues (Hueston et al., 2011) demonstrated that acute exposure to social stress was not effective in producing either peripheral or central inflammation. However, others have determined that a single exposure to social stress can promote enhanced neuroinflammation in response to a subsequent stress exposure (Audet et al., 2011). One explanation for this time-dependent phenomenon is neuroinflammatory priming, which is the mechanism whereby exposure to stress sensitizes microglia and as a result, facilitates the release of cytokines when challenged to a subsequent stressor. This phenomenon is not further discussed in the context of our review; however the topic is reviewed by Frank et al. within this special issue.

6. The role of inflammation in promoting depressive-like behavior

It is equivocal as to whether inflammation causes depression or if it is merely a consequence of a depressive episode. However, there is considerable evidence to point towards a causative role for inflammation. The most convincing findings are that compounds that promote inflammation are recognized to promote depression. Providing insight to this causative relationship, administration of interferon (IFN)-γ, granulocyte macrophage colony stimulating factor (GM-CSF), and IFN-α has been recently studied as a potential treatment for various cancers (Capuron et al., 2001; Schmeler et al., 2009). Of the many side effects associated with these treatments is the development of transient depressive episodes in patients with no prior history of depression (Capuron et al., 2001; Schmeler et al., 2009). In addition, as discussed at length in this review, exposure to psychosocial stressors that are capable of acutely and chronically elevating inflammation also precipitate depressive disorders (Danese et al., 2008). Furthermore, epidemiological studies have demonstrated that elevated inflammatory markers can be predictive of developing depression (Kim et al., 2009; Felger et al., 2013; Eraly et al., 2014). Based on these findings, researchers have proposed that inflammation could be causative rather than merely a result of suffering from depression. Indeed, using animal models, it has been shown that stimulation of the immune system either through injection of LPS, administration of pro-inflammatory cytokines, or inducing a bacterial infection can result in neuroinflammation (O’Connor et al., 2003; Johnson et al., 2004; Ji et al., 2014; Zhang et al., 2014; Biemans et al., 2015) and the development of depressive-like behavior as evidenced by behavioral despair (O’Connor et al., 2003; Ji et al., 2014; Zhang et al., 2014; Zhu et al., 2015) or anhedonia (Kaster et al., 2012; Ji et al., 2014; Zhang et al., 2014). Importantly, studies from our lab have highlighted the causal role that cytokines play in social stress–induced depressive-like behavior as blocking IL-1β in the brain prior to each daily exposure to social stress had no effect on the individual differences in coping strategy, however it prevented the development of anhedonia in susceptible rats (Wood et al., 2015). The specific roles that cytokines play in discrete brain regions are beginning to be unraveled and point towards cytokines affecting neurochemicals and neuronal activation of specific brain regions. The concept that inflammation may mediate the development of depressive behavior by altering central neurotransmitter activity and the firing rates of key brain regions is discussed in detail later in this review (see Section 8).

7. Stress-induced neuroinflammation as a vehicle for promoting depression-CVD comorbidity

It was first noted by Maltzberg almost 80 years ago, that patients suffering from depression were at increased risk of mortality (Maltzberg, 1937). In recent years there is an unmistakable association between stress-related psychosocial disorders and cardiovascular disease, revealing a mechanism for the increased mortality in depressed patients (Seligman and Nemeroff, 2015). Considerable evidence points towards the role that passive stress coping may play in susceptibility to depression, thereby linking passive stress coping with increased susceptibility to CVD. In fact, independent of depressive measures, some evidence exists for the role of passive stress coping in increased vulnerability to hypertension (Harburg et al., 1964) and psychosocial stress is also capable of promoting atherosclerosis (Black and Garbutt, 2002), likely mediated in part by inflammatory leukocytes (Heidt et al., 2014). Because inflammation plays a key role in the pathogenesis of both hypertension (Savoa and Schiffrin, 2006) and atherosclerosis (Black and Garbutt, 2002), inflammatory mediators lie at the intersection between depression and CVD and under conditions of stress, may promote the comorbidity between these two disorders. The link between inflammation in the peripheral tissues or plasma and CVD is not a novel concept and has been reviewed extensively. Therefore in this review we will focus on how changes in neuroinflammation have the potential to impact on neurotransmitters or neuropeptides within the brain to mediate neurogenic mechanisms that could promote CVD.

Animal studies have revealed a role for central inflammation in cardiovascular responses as injection of IL-1β in the brain increases blood pressure (Ye et al., 2000). Furthermore, centrally administered IL-1ra blunts the pressor response to air jet stress and footshock. In addition, the role of brain IL-1β in this stress-induced pressor response was confirmed by revealing that intravenous injection of IL-1ra was ineffective (Zou et al., 2001; Ufnal et al., 2008). In support of the role of endogenous IL-1β in depression-CVD comorbidity, we have identified that the susceptible (passive coping)
phenotype that exhibited increased IL-1β in the LC also displayed significant decreases in resting heart rate variability, indicative of increased sympathetic activity and decreased parasympathetic tone (Wood et al., 2012). Importantly, these changes in heart rate variability are evident in depressed patients and are known to be an independent risk factor for cardiac mortality (Carney et al., 1995). More recently, within our lab we have also identified that stress susceptible rats exhibit persistent increases in resting blood pressure throughout the 12-hr dark cycle compared with controls and their resilient counterparts (Lombard et al., unpublished results). Given that this is the same model that we reported increased IL-1β present in the brains of susceptible rats, it highlights an association between stress-induced increases in endogenous IL-1β and increased blood pressure (Fig. 1). While the direct role of central IL-1β in hypertension is unclear, Section 8 of this review attempts to elucidate how inflammation within the brain could impact on neurobiological substrates that could contribute to exaggerated CVD risk.

8. Effect of neuroinflammation on neurobiologic substrates underlying depression and cardiovascular control

The pathogenesis of stress-related psychiatric disorders and comorbid cardiovascular disease is multifaceted and may likely be a result of a complex interaction between stress-sensitive neuropeptides/neurotransmitters and inflammation. Although several lines of evidence support the hypothesis that increased inflammation may be causal to depression and CVD, it is not yet understood whether inflammatory factors also initiate the many neurobiological changes accompanying these disorders. Central nervous system alterations of serotonin (5-HT), norepinephrine (NE), corticotropin-releasing factor (CRF), and brain derived neurotrophic factor (BDNF) have all been documented in subsets of depressed patients and many of these have a cardiovascular impact. Once they reach the brain, either through primary production or passage to the brain from the periphery, inflammatory factors can regulate levels of each of these neurotransmitters/neuropeptides and therefore serves as a putative mechanism by which changes in inflammation may promote susceptibility or resilience to psychiatric disorders (Fig. 2). In many cases there is a bidirectional relationship between these neuropeptides/neurotransmitters and

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**Fig. 1.** Behavioral and physiological stress-related consequences are unique to the coping strategy adopted during social defeat. Consistent with the strategies humans use to cope with stress, rodents have also been shown to demonstrate distinct differences in the behavioral coping response to social stress. Phenotype: Individual differences in the phenotypic response to stress, such as demonstrating active (upright postures, resisting attacks) versus passive (rapid supine postures in presence of resident) coping responses, are associated with differing stress-related consequences. Inflammatory consequences: Passive coping rats exhibit an imbalance towards pro-inflammatory responses while active coping is related to a balanced inflammatory system. Behavioral consequences: Passive coping rats display anhedonia following social stress exposure, while active coping rats maintain hedonic behavior. Cardiovascular consequences: Exposure to social defeat stress in passive coping rats manifests cardiovascular dysfunction as evidenced by a decrease in heart rate variability and increased resting blood pressure. Active coping is related to normal cardiac function in the face of 5–7 days of repeated social defeat stress.
inflammation, however, for the purposes of this review we have focused on the impact that inflammatory factors have on these systems. In addition, central injections of cytokines (ie., IL-1β) are capable of producing cardiovascular responses, including increased blood pressure (Ye et al., 2000). Therefore, within each section we also review literature on how these inflammation-driven neurobiological changes may contribute to CVD.

8.1. Serotonin

The role of the serotonin system in the pathogenesis of depression has been the basis of scientific studies for over 40 years (Mendels et al., 1972; Mendels and Frazer, 1974). Studies measuring monoamines in the CSF of patients treated with cytokines have revealed that tryptophan levels in CSF are correlated with serotonin metabolites (Raison et al., 2009). A prominent effect of cytokines within serotonergic-rich regions is the activation of indoleamine-2,3-dioxygenase (IDO), an enzyme expressed in microglia, astrocytes, and neurons (Pemberton et al., 1997; Guillemin et al., 2005; Fujigaki et al., 2006) that catabolizes tryptophan, the amino-acid precursor to 5-HT, into kynurenine (KYN). As a result, IDO deactivates the activated receptor, phosphorylated TrkB. We hypothesize that a milieu of elevated inflammation initiates a cascade of adaptations within these stress sensitive systems to contribute to a susceptible phenotype that is primed to develop depression and CVD. (B) In the event that stress exposure does not result in persistent increases in inflammation, these neurobiologic systems remain largely unaffected, thereby protecting the individual. *It should be noted that the depicted inflammation-induced changes in BDNF represent the most simplistic of interpretations and in fact, certain changes in BDNF are more likely to be region specific.

**Fig. 2. Impact of neuroinflammation on stress-sensitive neurobiologic molecules.** Inflammatory cytokines have several documented effects on various neurobiological substrates related to depression and CVD. (A) Inflammation has largely stimulatory effects on CRF and NE while it generally serves to suppress 5-HT and BDNF along with BDNF's inhibitor in susceptible rats following social defeat. Specificaly, CRF administration onto 5-HT cells in the DR resulted in 5-HT neuronal inhibition in susceptible rats while this same dose of CRF produced a robust excitatory effect in 5-HT cells of resilient rats (Wood et al., 2013). While we confirmed that this was attributed to changes in trafficking of the CRF receptor, it should be noted that resilient rats also exhibit significant decreases in IL-1β in the DR (Wood et al., 2015) which may have contributed to the excitatory response of serotonergic cells by removing IL-1β inhibitory GABAergic tone in the DR of active coping rats. Taken together these clinical and preclinical studies point towards a role for inflammation impacting the serotonin system in a manner relevant to the pathogenesis of depression.

8.1.1. 5-HT's central regulation of cardiovascular control

In addition to its role in cytokine-induced depression, IDO activity also correlates with risk of CVD such as atherosclerosis (Pertovaara et al., 2007). Furthermore, depressed patients with CVD not only exhibit elevated inflammation, but also exhibit increased activation of the KYN pathway (Nikkeslat et al., 2015). These studies did not assess kynurenine or IDO levels in the brain, however this suggests that altered tryptophan catabolism may be involved in CVD. 5-HT also has direct cardiovascular effects within the brain and the effects are highly brain region and receptor subtype specific. For example, agonist activation of the 5-HT1A receptor in the dorsal raphe nucleus produces vagally-mediated bradycardia and hypotension (Connor and Higgins, 1990). Furthermore, microinjection of 8-hydroxy-DPAT, a 5-HT1A agonist, into the medullary raphe attenuates stress-induced tachycardia and pressor responses (Nalivaiko et al., 2005; Ngampramuan et al., 2008). Alternatively, central 5-HT2C receptors have been
demonstrated to regulate, in large part, the pressor response during restraint stress in rats (Ferreira et al., 2005) in the nucleus tractus solitarius. Furthermore, 5-HT3 receptors located within the sympathetic ganglia may likely regulate stress-induced hypertension (Alkadi et al., 1996). 5-HT central control of stress-induced cardiovascular responses is highly complex and has been thoroughly reviewed by (Nalivaiko and Sgoifo, 2009). Taken together, inflammation has demonstrated ability to alter the 5-HT system in the brain, and is therefore yet another inflammation-sensitive neurotransmitter that has the capacity to promote comorbidity between depression and CVD either through altered receptor activation or shifts in tryptophan catabolism via the IDO/kynurenine pathway.

8.2. Norepinephrine

The original catecholamine hypothesis of major depression suggested that depression was associated with NE deficiency; however more recent findings of melancholic depressed patients suggest the contrary. For example, CSF levels of NE were found to be elevated in depressed patients over that of non-depressed patients (Roy et al., 1985) and these results were confirmed for hourly intervals for 24 h a day (Wong et al., 2000). A rise in central NE was paralleled by elevated NE levels in the plasma and both central and peripheral NE normalized after successful treatment with electroconvulsive therapy (Gold et al., 2005). Although there is support for absolute changes in NE levels promoting psychiatric disorders (i.e., melancholic depression) it is more likely that a dynamic dysregulation of this system contributes to stress-related psychiatric disorders. Alterations in the number and distribution of NE transporters have been identified and alterations in receptor binding have also been related to depression (Ressler and Nemeroff, 2000). To our knowledge, concomitant measurements of cytokine and NE levels in CSF of depressed patients or measurement of NE levels in patients treated with cytokines have not been conducted. However, a positive correlation between IL-6 levels and NE has been demonstrated in PTSD patients, another psychosocial disorder that is frequently associated with elevated inflammation (Baker et al., 2001).

Animal studies have shed light on the direct effect of cytokines on central NE levels. While proinflammatory cytokines have been shown to have an inhibitory effect on NE in brain regions regulating reproduction, several reports indicate that cytokines increase NE levels in stress-related brain regions. For example, IL-1β or IL-2 increased NE levels in stress-associated brain regions such as the central nucleus of the amygdala, paraventricular nucleus and prefrontal cortex (Lacosta et al., 2000; Sirivelu et al., 2012). One manner by which cytokines could stimulate NE levels in the brain is by direct effects on LC-NE neurons, the major source of NE to the brain. Microinjection of IL-1β or LPS into the LC increases the activity of these noradrenergic neurons (Borsody and Weiss, 2002, 2004) and the effect of LPS injection increased LC neuronal activity for at least 7 days after a single injection (Borsody and Weiss, 2004). Increased LC activity following cytokine administration likely results in concomitant release of NE to the expansive network of LC targets within the brain. Interestingly, a susceptible subset of socially defeated rats exhibit elevated cytokine levels in the LC (Wood et al., 2015) and a recent publication from Reyes and colleagues using this same social defeat model revealed increased defeat-induced LC activity in susceptible rats (Reyes et al., 2015). Treatment with an IL-1 receptor antagonist has been shown to not only reverse the LPS-induced increase in spontaneous discharge rate (Borsody and Weiss, 2002, 2004) but also prevents the emergence of defeat-induced depressive-like behavior (Wood et al., 2015), further supporting the role of endogenous IL-1β in stress-induced depressive-like responses. In sum, cytokines have discrete and dynamic effects on NE synthesis and release, which may drive various aspects of stress-related psychiatric disorders.

8.2.1. LC-NE’s central regulation of cardiovascular control

Historically studies have been equivocal regarding the functional effect of LC-NE activation on peripheral cardiovascular activity. With peptidergic-induced activation or electrical stimulation of LC-NE neurons reported to elicit increased sympathetic nervous system activity (Crawley et al., 1980; Brown, 1986; Paakkari et al., 1987), while chemical activation of LC neurons either suppressed (Sved and Felsten, 1987) or increased blood pressure (Chen and Huang, 1997). We now understand these conflicting findings likely arose in part from differences in rodent strains, awake versus anesthetized animals, or different types of anesthesia (Kawamura et al., 1978; Sved and Felsten, 1987; Chen and Huang, 1997). More recent advances using optogenetic stimulation of LC-NE neurons revealed a direct inhibition of the cardioinhibitory vagal neurons within the dorsal motor nucleus of the vagus (Wang et al., 2014). Furthermore, the nucleus ambiguous also reduces heart rate and blood pressure by suppressing the sympathoexcitatory rostroventrolateral medulla (McKirdy and Calaresu, 1996). Similar to the dorsal motor nucleus, the LC also projects to the nucleus ambiguous and inhibits its activity (Jones and Yang, 1985; Samuels and Szuhadi, 2008b, c) thereby removing the inhibitory influence over the rostroventrolateral medulla. Optogenetic activation of astrocytes was used to promote the release of L-lactate into the LC, thereby activating LC-NE neurons. Furthermore, this study revealed that activation of LC-NE neurons by L-glutamate or L-lactate increased heart rate and blood pressure (Tang et al., 2014). Therefore, as functional evidence of the combined effects of the excitatory influence on sympathetic neurons and inhibitory influence on parasympathetic neurons, selective stimulation of LC-NE neuronal projections as produced by IL-1β, can result in peripheral catecholamine release and increased heart rate and blood pressure (Kawamura et al., 1978; Gurtu et al., 1984; Drolet and Gauthier, 1985). Therefore, persistent elevations in central IL-1β that serve to increase LC firing could promote comorbid hypertension and depressive-like responses, representing another mechanism by which inflammation can promote the pathogenesis of both depression and CVD.

8.3. Corticotropin-releasing factor

Corticotropin-releasing factor (also called corticotropin-releasing hormone) is a stress-sensitive neuropeptide that is expressed ubiquitously throughout the central nervous system (Owens and Nemeroff, 1991). Since its discovery by Wiley Vale and colleagues in 1981 (Vale et al., 1981), CRF has become known for its role in nearly every stress-related response, from stress-induced endocrine responses, to behavior and cardiovascular responses (Bale and Vale, 2004; Wood and Woods, 2007). Evidence from clinical studies indicates that CRF is increased in the CSF of depressed patients, implicating CRF in the pathogenesis of depressive disorders (Nemeroff et al., 1984; Arborelius et al., 1999; Holsboer and Ising, 2008). Importantly, inflammation has a facilitative effect on the CRF system. For example, inflammation increases activation of the hypothalamic pituitary adrenal axis, the neuroendocrine pathway that is initiated by CRF (Calogero et al., 1988). This effect is driven, in part by CRF, because a CRF antagonist blocks the stimulatory effect of IL-6 and TNF-α on the HPA axis (van der Meer et al., 1996). In addition, studies have identified that IL-6 is co-expressed with CRF within the paraventricular nucleus (Gorbel et al., 2003) and IL-6 produced within this region stimulates CRF gene expression (Kageyama and Suda, 2009). Interestingly, post mortem studies revealed increased CRF-immunoreactive neurons in the paraventricular nucleus of
depressed patients compared with controls (Raadsheer et al., 1994). While this study did not measure immune factors within this region, it begs the question as to whether or not elevated cytokines can promote the increased CRF levels observed in the depressed patients. In addition, although outside the scope of this review, it should be noted that CRF is the initiating factor in the hypothalamic pituitary adrenal axis that stimulates the release of glucocorticoids. Although it is unknown whether inflammation can alter glucocorticoid release or function, glucocorticoids have been shown to play a role in neuroinflammatory priming (Frank et al., 2015).

8.3.1. CRF's central regulation of cardiovascular control

Central CRF also represents another stress-sensitive neuropeptide that serves the dual purpose of promoting depressive and anxiety-like behaviors and regulating cardiovascular activity (Wood and Woods, 2007). Central injections of CRF are well recognized as producing a marked pressor response and tachycardia (Briscoe et al., 2000; Nijssen et al., 2000) and CRF overexpressing mice exhibit increased heart rate and decreased heart rate variability (Dirks et al., 2002). Exaggerated central CRF tone has also recently been identified in stress susceptible socially defeated rats (Reyes et al., 2015). Retrograde labeling studies were conducted in response to 5 daily social defeat exposures and revealed that stress susceptible rats exhibited increased activity of LC-projecting CRF neurons in the central amygdala above that of control and resilient rats (Reyes et al., 2015). It is unknown, however, whether increased inflammation occurred in the central amygdala within this subset of rats to produce the increase in CRF or whether cardiovascular function was altered as a result. None-the-less, while CRF serves to activate LC neurons this may be another mechanism by which stress increases LC-NE activity in stress susceptible rats. Taken together, stress-induced changes in the CRF system represents yet another mechanism by which inflammation may impact on a neuropeptide system that is capable of producing both depressive-like behaviors and CVD.

8.4. Brain-derived neurotrophic factor

BDNF is a growth factor traditionally associated with neuronal cell growth, function, and learning; furthermore, it has also been associated with the regulation of serotonin, choline, and dopamine (Russo-Neustadt, 2003; Pivac et al., 2012). In addition, stress has reliably been shown to alter the central expression of BDNF, while antidepressants increase its expression (Duman and Monteggia, 2006; Castren et al., 2007; Schmidt and Duman, 2007, 2010). In social defeat models, stress exposure has been demonstrated to alter BDNF in a region specific manner with both decreases and increases in BDNF being related to the development of depressive-like behaviors (Berton et al., 2006; Patki et al., 2013; Der-Avakian et al., 2014; Zhang et al., 2015). This region specificity becomes even more complex when individual differences are considered; rodents that were classified as resilient to social stress exhibit robust increases in BDNF and decreases in the inactive BDNF receptor (Tyrosine receptor kinase B, TrkB, type 1) expression in the hippocampus, while changes in BDNF are lacking in susceptible rats (Duclot and Kabbaj, 2013). Interestingly, Duclot and Kabbaj went on to inhibit BDNF signaling in the hippocampus of a resilient subset of rats, which rendered their behavioral consequences comparable to the susceptible subset of rats. Alternatively, Berton et al. (2006) reported that ventral tegmental area-specific deletion of BDNF in mice blocked social aversion following social defeat stress resembling the effects of chronic antidepressant treatment, which rendered the same reduction in BDNF within this brain region. These conflicting accounts likely demonstrate the complex, region specific nature of the role of BDNF in stress susceptibility. Although the role of cytokines in stress-induced BDNF responses is unclear, acute LPS injection functions to decrease the concentration of BDNF and the phosphorylation state of BDNF’s receptor, TrkB, as well as produce morphological changes in the hippocampus and prefrontal cortex evidenced by decreased spine density (Zhang et al., 2015; Zhu et al., 2015).

8.4.1. BDNF's central regulation of cardiovascular control

The BDNF-TrkB signaling pathway typically serves to promote cell survival and neuronal plasticity, however it has also been suggested that dysfunction in its signaling cascade can increase the spontaneous firing rate of the central amygdala (Ming et al., 2013; Prager et al., 2013), a brain region critical for the behavioral and cardiovascular responses to stress. The role of stress-induced changes in BDNF within the brain in the context of cardiovascular disease is largely unexplored, however it has been determined that peripheral levels of BDNF play a significant role in stroke recovery (Abramenko Lu et al., 2015; Chan et al., 2015) and contribute to increased risk of heart failure (Takahashi et al., 2015). Based on these data, there is a strong need to understand the role that stress-induced alterations in BDNF-TrkB signaling within the brain play in not only depression but also cardiovascular disease.

9. Therapeutic relevance

Throughout this review we have utilized the current experimental evidence to outline the putative role of neuroinflammation in depression and it’s high rate of comorbidity with CVD. Paradoxically, antidepressant therapies, such as tricyclic antidepressants, can in fact increase vulnerability to CVD due to the inherent cardiotoxic effects of these drugs, not a consequence of alleviating depression (Cohen et al., 2000). More recently, a clinical study has revealed that antidepressant therapy in general is cardioprotective over a 3-year period of time in patients with moderate to severe depression but not in patients with mild depression (May et al., 2015). Traditional antidepressant therapies such as monoamine oxidase inhibitors, selective serotonin and norepinephrine reuptake inhibitors, and tricyclics function to reduce depressive scores in a majority of depressed patients; however, these traditional treatments do not or only moderately reduce the inflammation present in the sub-population which exhibit increased inflammation (Maes et al., 1997; Sutcliffe et al., 2007; Uher et al., 2014). Animal studies have largely supported these findings. For example, Fluoxetine blocks social stress or LPS-induced depressive behavior (Kaster et al., 2012), while the resulting inflammation is only modestly attenuated (Ji et al., 2014; Li et al., 2015; Zhu et al., 2015).

Due to the putative role of inflammation in both depression and CVD, therapies that serve to reduce neuroinflammation may be beneficial in select patient populations. For example, treatment with Infliximab, a TNF-α antagonist, has been shown to reduce both depressive scores and inflammation in the treatment resistant subset of patients with high baseline inflammation (Raison et al., 2013). These data suggest that for this sub-population of depressed patients it may be justified to further explore the antidepressant efficacy of anti-inflammatory compounds or use an anti-inflammatory agent as an adjuvant to traditional therapies. Although clinical data are lacking on the efficacy of natural anti-inflammatory compounds in the treatment of depression, several studies using human cell lines have found that resveratrol, one of the more commonly used natural anti-inflammatory agents, can effectively block stimulated inflammation (Manna et al., 2000; Falchetti et al., 2001; Donnelly et al., 2004; Kang et al., 2009). Furthermore, animal studies demonstrated that natural anti-inflammatory agents, such as apigenin (Li et al., 2015), salidroside (Zhu et al., 2015),...
perillaldehyde (Ji et al., 2014), and resveratrol (Xu et al., 2010; Ahmed et al., 2014; Hurley et al., 2014), exhibit antidepressant-like effects. These agents generally function to reduce inflammation by blocking the expression of inflammatory progenitors (NF-κB: Zhu et al., 2015; COX-2, iNOS: Li et al., 2015), but have also been shown to increase the amount of serotonin and norepinephrine available in the brain (Xu et al., 2010; Ahmed et al., 2014; Ji et al., 2014; Zhu et al., 2015). It should also be noted that diet and exercise can significantly influence the immune system and therefore lifestyle changes may also be useful therapy for inflammation-related psychiatric disorders and cardiovascular disease (reviewed in Nahrendorf and Swirski, 2015). Based on these findings, natural therapies with anti-inflammatory efficacy may represent a useful alternative therapeutic or adjuvant for depressed patients who present with elevated inflammation and may likely reduce CVD risk.

10. Conclusion

While depression is no doubt a heterogeneous disorder that likely presents with varied pathological mechanisms, there is a compelling relationship between psychiatric disorders and inflammation (Raison et al., 2006). A great deal of focus has been directed towards understanding whether elevated inflammation is causal to depression or whether it occurs merely as a result of the myriad of physiological alterations that accompany a depressive episode. Several lines of evidence presented in this review suggest that inflammation may be causal to depressive illness. For example, the Whitehall II study revealed that inflammatory markers predict depressive symptoms over a 12-year follow-up (Gimeno et al., 2009). Furthermore, administration of pro-inflammatory agents induces depressive symptoms in patients with no history of depression and in laboratory animals (O’Connor et al., 2009b; Schmeler et al., 2009; Kaster et al., 2012; Ji et al., 2014; Zhu et al., 2015). Based on the widespread studies evaluated in this review, susceptibility to social stress is characterized by an environment of enhanced inflammation and may represent a mechanism promoting the comorbidity between depression and CVD (Miller et al., 2002). We put forth the hypothesis that a unique milieu of neuroinflammation in the context of repeated stress exposure impacts stress-sensitive neurotransmitters/neuropeptides to promote increased sensitivity to depression and co-morbid cardiovascular disease. Carefully designed in vivo studies are needed to provide further evidence that exaggerated pro-inflammatory cytokines trigger the shared pathophysiology resulting in depression-CVD comorbidity.

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