Send Orders for Reprints to reprints@benthamscience.net

Current Neuropharmacology, **2014**, *12*, **205-211**

Individual Differences in the Neurobiology of Social Stress: Implications for Depression-Cardiovascular Disease Comorbidity

Susan K. Wood*

University of South Carolina School of Medicine, Department of Pharmacology, Physiology and Neuroscience

Abstract: Stress initiates a cascade of complex neural and peripheral changes that promote healthy adaption to stress, but when unabated, leads to pathology. Fascinating individual differences arise in the ability to cope with a stressor, rendering an individual more or less likely to develop stress-induced pathologies such as depression, anxiety, and cardiovascular disease. In this review we evaluate recent findings that investigate the neural underpinnings of adopting a passive or active coping response during social defeat stress. Because passive coping is associated with vulnerability to stress-related pathologies and active coping confers resiliency, understanding neurobiological adaptations associated with these diverse coping strategies may reveal biomarkers or targets impacting stress susceptibility. The co-occurrence of stress-induced depression and cardiovascular disease is becoming increasingly clear. Therefore this review focuses on the central mechanisms capable of contributing to psychopathology and cardiovascular disease such as corticotropin releasing factor, neuropeptide Y, monoamines, cytokines and oxidative stress. The impetus for this review is to highlight neurobiological systems that warrant further evaluation for their contribution to the pathophysiology of depression-cardiovascular disease comorbidity.

Keywords: Resident-intruder paradigm, coping, corticotropin releasing factor, locus coeruleus, dorsal raphe.

INTRODUCTION

The inability to successfully cope with a stressor produces pathological changes that can lead to psychological disorders such as depression and anxiety as well as medical diseases including diabetes, irritable bowel syndrome and cardiovascular disease [1-3]. As such, stress imposes a hefty price tag costing US industries an estimated $300 billion annually as a result of absences, employee turnover, diminished productivity and medical and insurance costs [4, 5]. The association between stress-related psychological disorders and cardiovascular disease is unmistakable; depression significantly increases the risk of cardiac morbidity and mortality and cardiovascular disease also increases risk of depression [6-8]. It is recognized that persistent sympathetic activation may contribute to depression, PTSD and increased risk for hypertension and cardiovascular disease [9, 10], however the neurobiological mechanisms associated with comorbid psychiatric and medical disorders remain unclear. As such, the identification of biomarkers or mechanisms associated with the intersection between the mind and body could provide insight to the shared etiology of these disorders.

Stressors of a social nature are the most common type of stress encountered by humans, including abuse and bullying [11], and are implicated in the pathogenesis of depression and cardiovascular disease [12-14]. There is great individual variability in the consequences of stress exposure, however the pathogenic potential of a stressor does not solely depend on the severity. In fact, the majority of individuals exposed to traumatic experiences or chronic social stress do not develop pathological outcomes. One feature that may be related to differential susceptibility to stress is the type of strategy used to cope with the stressor [15]. Interestingly, submissive personality traits or passively coping during chronic stress is associated with vulnerability to psychopathology [16, 17] and hypertension [18-20] while active coping is related to resiliency [21]. An ethologically relevant animal model that is useful for studying individual differences in susceptibility to social stress is the resident-intruder paradigm [22, 23]. This model involves exposing a male rat (intruder) to the aggressive threats of a larger, unfamiliar male rat (resident) by placing it in the resident's home cage for a short period of time [24]. Our recent work using the resident-intruder model highlights the association between passive coping and susceptibility to a depressive-like phenotype with cardiovascular dysfunction whereas proactive coping confers resiliency (Fig. **1**) [22, 25]. Neurotransmitters, neuropeptides, oxidative stress, and pro-inflammatory cytokines have been linked to the acute stress response and long-term pathogenic consequences. In this review we discuss the neurobiological adaptations associated with the passive and active coping response to social stress. Importantly, we focus on neural mediators that represent likely targets contributing to depressive-like behaviors and cardiovascular pathologies. The impetus for this review is to highlight neurobiological systems that warrant further evaluation for their contribution in the pathophysiology of depression-cardiovascular disease comorbidity.

*Address correspondence to this author at the University of South Carolina School of Medicine, Department of Pharmacology, Physiology and Neuroscience, Basic Sci Bldg 1, D28A, 6439 Garners Ferry Rd, Columbia, SC 29209, USA; Tel: (803) 216-3522; Fax: (803) 216-3549;
E-mail: susan.wood@uscmed.sc.edu

1875-6190/14 $58.00+.00

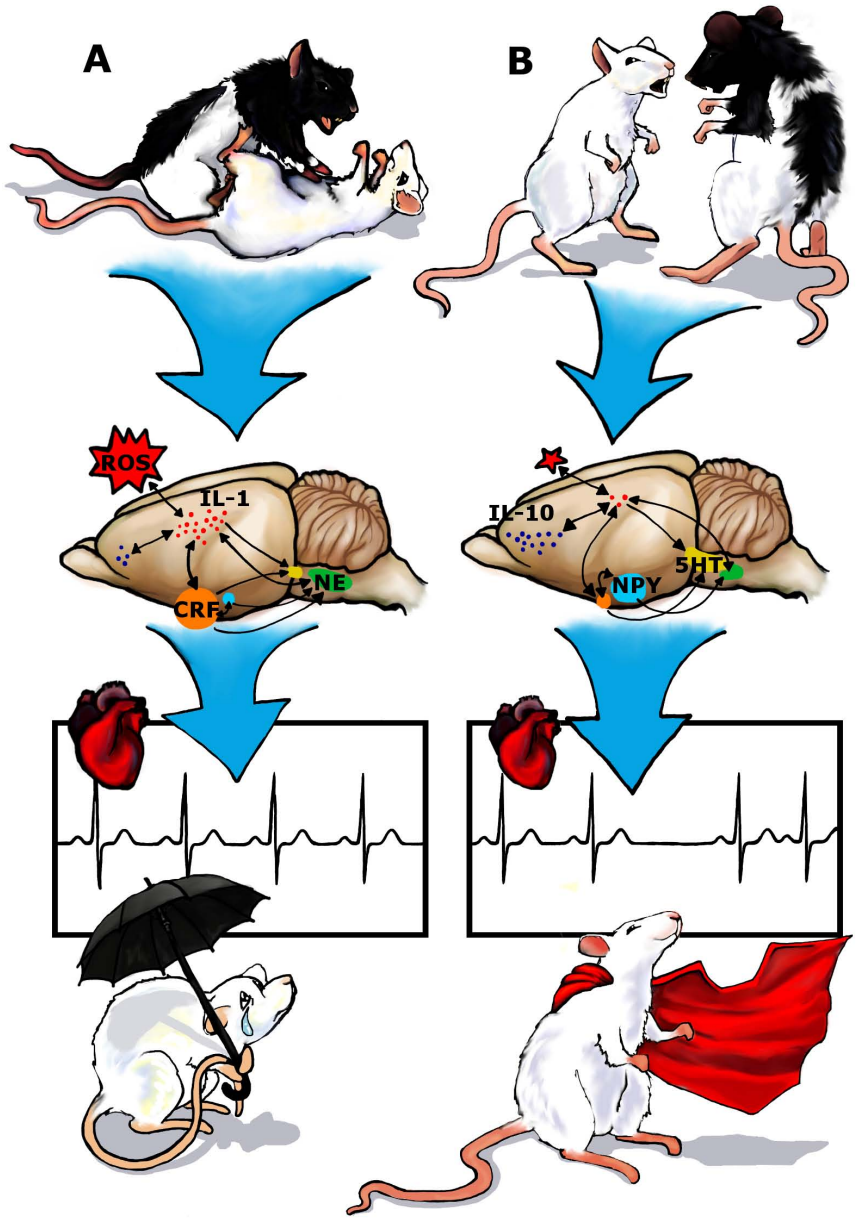

Fig. (1). Distinct consequences of passive and active coping during social defeat stress. Based on studies from our lab and others we postulate that rats characterized by a passive coping strategy (**A**) exhibit neurobiological adaptations leading to stress vulnerability and include increases in the CRF, noradrenergic, proinflammatory cytokine and oxidative stress systems. These stress-induced changes within the brain lead to reductions in heart rate variability (HRV), increased cardiac hypertrophy, and translate to a depressive-like phenotype. Alternatively, actively coping during social stress (**B**) leads to a distinct sequence of adaptions; stress results in reductions in the CRF and NE systems within the brain. Additionally, neuroinflammation and oxidative stress (ROS) is reduced and NPY and serotonergic systems are enhanced. These central changes promote resilience in the face of adversity and may prevent decreases in HRV and the development of depressive-like behaviors.

INDIVIDUAL DIFFERENCES IN STRESS COPING IMPACT THE CONSEQUENCES OF SOCIAL DEFEAT STRESS

As in humans, rodents exhibit individual differences in their reactivity and consequences to social stress. In an outbred population of Sprague Dawley rats we previously reported two distinct phenotypic responses to repeated social defeat using the resident-intruder paradigm [22]. One population exhibited passive coping behaviors and assumed a supine defeat posture within a short latency (termed SL). The other phenotype developed proactive coping behaviors as early as the third exposure to social defeat, indicated by upright postures and a resistance to display the supine defeat posture, resulting in a longer latency (LL). The passive SL phenotype was characterized by enhanced neuroendocrine activity, depressive-like behavior, and reduced resting heart rate variability (HRV) while the LL phenotype remained

generally resistant to these changes [22, 25]. Others have reported that one exposure to social defeat in singly housed rats produces a depressive-like state and cardiovascular alterations evident for weeks following stress exposure, however individual differences were not assessed [26]. In a related study, intruders adopting a proactive response to social stress (countering the resident's attacks) displayed smaller and shorter lasting disturbances of circadian heart rate rhythmicity following social stress compared to rats that adopted a more passive response [27]. These studies emphasize how a variation in coping response impacts the consequences of social stress, and highlight the association between passive stress coping and vulnerability to depressive-like behaviors and increased cardiovascular disease risk.

Different coping styles are not only characterized by separate behavioral responses to stress, but also a distinct neuroendocrine and physiological response. We recently reported that SL defeated rats exhibit exaggerated hypothalamic-pituitary-adrenal axis (HPA) reactivity during repeated social defeat as compared with the proactive LL rats, and an exaggerated HPA response to a novel stressor [22]. In support of our findings, another group compared the effect of a single social defeat on the neuroendocrine response and found a negative association between defensive guarding behaviors during defeat and corticosterone release [28]. Greater HPA activation observed in the passive coping rats likely promotes the consequence of endocrine dysfunction observed in the SL phenotype.

Distinct autonomic responses to stress are also related to differing coping styles; high sympathetic reactivity (ie. increased plasma NE, tachycardia and increased blood pressure) is associated with active coping responses while passive coping is associated with heightened parasympathetic responses during stress [29]. Despite this association, we identified exaggerated reductions in resting heart rate variability (HRV) in the passive SL rats 24-48 hours after repeated social stress. These data indicate that the stress susceptible SL phenotype exhibits exaggerated sympathetic and/or reduced parasympathetic activity under resting conditions [25]. Akin to our work, a study in which rats were classified as passive or active copers prior to chronic intermittent stress reported the association between passive coping and hypertension [30]. In contrast, dominant "active coping" rats living within a colony were reported to be vulnerable to persistent hypertension while the submissive rats were normotensive [31]. Studying submissive and dominant rats in an established colony greatly differs from intermittent social defeat stress whereby a rat is removed from its home cage and reintroduced into the home territory of a larger aggressive rat and is likely the cause of these discrepant results. Despite reports that passive-coping rats would exhibit less sympathetic activation during stress, our studies and others reveal exaggerated resting sympathetic activation as a consequence of passive stress coping. Therefore, in this case the physiological response during stress does not appear to directly contribute to the autonomic consequences. Alternatively, adaptations within the brain that are related to passive coping and central to depression and cardiovascular disease may shed light on the etiology of passive coping predisposing to elevated sympathetic activity and resulting depression-cardiovascular disease comorbidity.

CORTICOTROPIN RELEASING FACTOR (CRF) AND NEUROPEPTIDE Y (NPY)

Exposure to a challenge or "stressor" initiates a cascade of complex neural and peripheral mediators that comprise the stress response. The neuropeptide CRF is considered the hallmark of the stress response and is directly involved in stress-related emotionality [32, 33]. In extrahypothalamic regions of the brain such as the amygdala and locus coeruleus (LC), CRF receptor activation results in autonomic and behavioral features of the stress response [9, 34-36]. Like many elements of the stress response CRF is capable of promoting healthy adaptation to stress [32], but when unabated it may lead to pathology. Overproduction of CRF as evidenced by increased CRF in cerebrospinal fluid, increased immunoreactivity in the paraventricular nucleus (PVN), and the dorsal raphe (DR) have been associated with depressive disorders [37-39]. Given its widespread effects, exaggerated CRF activation in the brain is capable of contributing to the behavioral, neuroendocrine and cardiovascular effects associated with depression-cardiovascular disease comorbidity. CRF has previously been linked to social defeat-induced cocaine "binge", linking the CRF system with stress-induced drug abuse [40]. Consistent with findings of increased CSF levels of CRF linked to major depression in humans [41] evidence of HPA axis hyperactivity and exaggerated CRF release was identified in the passive SL phenotype [22]. To test the notion that CRF contributes to social stress-induced depression-cardiovascular disease comorbidity, we treated rats with the centrally acting CRF_1 antagonist NBI-30775 [25]. CRF_1 blockade shifted rats towards exhibiting the LL resilient phenotype; upright postures and defeat latencies were increased, behavioral despair in the forced swim test was inhibited, and neuroendocrine and cardiovascular consequences of social defeat were prevented by NBI-30775 treatment [25]. These results underscore the role of CRF in the development of stress-induced depression-cardiovascular disease comorbidity.

Neuropeptide Y is also widely distributed and expressed in brain regions rich with CRF such as the LC [42], PVN [43], and the amygdala [44] and is reported to oppose the effects of CRF [45, 46]. For example, CRF serves as an excitatory neurotransmitter in the LC [47] while NPY reduces the firing of noradrenergic neurons in the LC [48]. Evidence of elevated LC activity has been linked to depression [49, 50] and therefore NPY in the LC may promote stress resilience. The anti-stress effect of NPY, however, is not unique to the LC; decreased NPY was observed in the amygdala, hippocampus and periaqueductal gray of rats that were vulnerable to a predator-scent stress paradigm compared with the resilient phenotype [51]. Amygdalar NPY has also been shown to produce an anxiolytic effect in rodents [52]. Moreover, low levels of NPY are reported in PTSD patients [53]. Importantly, NPY also has hemodynamic effects; in contrast to CRF central administration of NPY lowers blood pressure and heart rate during social defeat in rats [54]. Along these lines, high levels of NPY were observed in highly resilient special

operations soldiers [55]. In these individuals robust increases in NE are regulated by equally robust increases in NPY. Therefore converging lines of evidence implicate NPY in the psychobiology of resilience to stress-induced depression and cardiovascular disease comorbidity.

CRF REGULATION OF MONOAMINES: NOREPINEPHRINE AND SEROTONIN

The LC-NE pathway is a major stress reactive system that is implicated in depressive disorders [49, 50]. As such, alterations in this CRF sensitive brain region may contribute to susceptibility to stress-induced pathologies. In a recent study from our group, the enduring impact of repeated social stress on LC neuronal activity in awake, behaving rats was characterized [56]. Forty-eight hours after a 5^{th} exposure to social stress, LC spontaneous discharge rate was decreased in the LL, resilient phenotype. Although rats from which LC recordings were obtained were only characterized by the LL phenotype, this study also identified stress-related receptor changes within the LC of the passive (SL) and active coping (LL) phenotypes. We concluded that decreased spontaneous LC neuronal activity in the LL phenotype was related to increased activation of mu opioid receptors (MOR), responsible for an inhibitory tone within the LC [57-59] and down-regulation of CRF_1 [56]. Receptor trafficking in the SL phenotype was distinct from LL rats and was characterized by greater CRF_1 localized in the cytoplasm, with no change in MOR. These results highlight distinct stress-induced changes within the LC-NE system that are related to stress susceptible and resilient phenotypes. Furthermore, these data emphasize a reduction in LC activity associated with a phenotype previously found to be resistant to depressive-like consequences [22], and is consistent with reports that antidepressant treatment reduces LC-NE activity [60, 61]. Although studies identifying the role of LC-NE activation on the peripheral sympathetic nervous system are equivocal, there is support for increased LC neuronal activity to result in a parallel increase in heart rate and blood pressure [62, 63]. Interestingly, the distinct stress-induced adaptations in the LC-NE system in the LL phenotype could not only contribute to decreased susceptibility to a depressive phenotype, but also serve as cardioprotective.

CRF also influences the serotonin (5-HT) containing DR [64], another monoaminergic system linked to depressive disorders. Unlike the LC where only CRF_1 receptors are present, the DR contains both CRF_1 and CRF_2 receptor subtypes [65] that have opposing effects on 5-HT neuronal activity. At low doses CRF preferentially binds CRF_1, which increases gamma-aminobutyric acid (GABA)-ergic inhibition of DR-5-HT neurons and decreases extracellular levels of 5-HT in forebrain and limbic targets [66-68]. At higher doses, CRF binds to CRF_2 and excites 5-HT neurons, thereby increasing extracellular 5-HT in forebrain and limbic targets [65-72]. Importantly, the distribution of CRF receptors within the DR-5-HT system is influenced by prior stress exposure [65]. Recent reports from our lab reveal recruitment of different CRF receptor subtypes in the SL and LL phenotypes, leading to qualitatively different cellular responses to CRF and ultimately divergent consequences [73]. In response to repeated social defeat stress, only active coping rats exhibited dynamic adaptations within the DR. In these rats, social stress promoted a shift from CRF_1 located predominantly on the plasma membrane, as is observed in controls and SL rats, to recruitment of CRF_2 to the cell surface [73]. This cellular adaptation in LL rats promoted CRF-induced 5-HT neuronal firing [73], promoting the release of extracellular 5-HT in DR targets [67, 69]. Alternatively, a lack of adaptation in the SL phenotype resulted in CRF-induced 5-HT neuronal inhibition, likely resulting in decreased serotonin release in DR targets. Together with reports of decreased 5-HT function in depressed patients including decreased levels of 5-HT and its metabolites in CSF and brain tissue [74, 75], these studies indicate that adaptations within the CRF system in the DR may protect against a hyposerotonergic state, thereby promoting resilience. Furthermore, central 5-HT has extensive cardiovascular effects [76]. As a result, eliciting dynamic adaptations within the central serotonergic system may impact susceptibility to a depression-cardiovascular disease state.

OXIDATIVE STRESS AND PROINFLAMMATORY CYTOKINES

Induction of oxidative stress in the brain is reported to produce anxiety- [77-79] and depressive-like [80, 81] responses in rodents. Importantly, induction of oxidative stress in the brain is also associated with hypertension [77]. Recently, the impact of social stress on biomarkers of oxidative stress within the brain was reported [81]. While individual differences in the behavioral coping response to social stress was not studied, increased levels of anhedonia within the social stressed group corresponded to reduced antioxidant defense and greater oxidative stress [81]. Thus, social stress elicits depressive-like behaviors that are positively correlated with the extent of oxidative stress occurring in the brain.

Inflammation has long been recognized as contributing to cardiovascular disease and recent evidence implicates inflammatory factors in the pathogenesis of depression. Patients suffering from depression exhibit increased levels of the proinflammatory cytokine IL-6 at rest and greater social stress-induced IL-6 levels, which are normalized following antidepressant therapy [82-84]. Interestingly, people displaying fewer active coping behaviors exhibit greater immune (IL-6) response to stress [85]. Preclinical data also support the role of inflammation in depressive-like behaviors; IL-6 knockout mice demonstrate decreased depressive-like behaviors [86]. Social defeat has been reported to increase the proinflammatory cytokine IL-6 within the hippocampus, however individual differences related to coping or vulnerability has not been evaluated. Alternatively, a study of chronic psychosocial stress in mice reported decreased IL-1β and TNF-α in the hippocampus [87]. Despite these equivocal reports, a growing, yet still poorly understood body of evidence points towards neuroinflammation in the psychopathology of stress-related disorders [88-90]. Given the association between social stress-induced accumulation of reactive oxygen species (ROS), neuroinflammation, depression, and hypertension a synergistic relationship between oxidative stress and inflammation may likely contribute to depression-cardiovascular disease comorbidity and warrants further investigation.

This review highlights several cellular adaptations that occur in response to social defeat stress illustrating that the same stressor can evoke divergent consequences promoting resilience in one individual and vulnerability in another (Fig. **1**). Studying distinct neurobiological adaptations that occur in response to passive or active stress coping may illuminate the pathophysiology of vulnerability and resiliency to social stress. Moreover, by focusing this review on the central mechanisms capable of contributing to psychiatric disorders and cardiovascular activity, we have highlighted neurobiological systems that may underlie the pathophysiology of the comorbidity between depression and cardiovascular disease. A thorough characterization of these neurobiological mediators using a social stress model that independently characterizes susceptibility will be an important advance in predicting and treating stress-induced depression and cardiovascular disease comorbidity.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The author would like to graciously thank Victoria Macht for her creative contribution of Fig. (**1**). Source of funding for the manuscript preparation was NARSAD Young Investigator grant #17830 and AHA grant #13BGIA14370026.

REFERENCES

[1] Campayo, A.; Gomez-Biel, C.H.; Lobo, A. Diabetes and depression. *Curr. Psychiatry Rep.*, **2011**, *13*(1), 26-30.PMID: 21052874

[2] Fenton, W.S.; Stover, E.S. Mood disorders: cardiovascular and diabetes comorbidity. *Curr. Opin. Psychiatry*, **2006**, *19*(4), 421-427. http://dx.doi.org/10.1097/01.yco.0000228765.33356.9f

[3] Folks, D.G. The interface of psychiatry and irritable bowel syndrome. *Curr. Psychiatry Rep.*, **2004**, *6*(3), 210-215. http://dx.doi.org/10.1007/s11920-004-0066-0

[4] Stress, A.I.o. In: http://www.stress.org/workplace-stress/.

[5] Goldin, R. Counting the costs of stress. In: http://www.stats.org/stories/2004/counting_costs_stress_sep23_04.htm; 2004. http://dx.doi.org/10.1016/0021-9681(64)90101-8

[6] Rugulies, R. Depression as a predictor for coronary heart disease. a review and meta-analysis. *Am. J. Prev. Med.*, **2002**, *23*(1), 51-61. http://dx.doi.org/10.1016/S0749-3797(02)00439-7

[7] Surtees, P.G.; Wainwright, N.W.; Luben, R.N.; Wareham, N.J.; Bingham, S.A.; Khaw, K.T. Depression and ischemic heart disease mortality: evidence from the EPIC-Norfolk United Kingdom prospective cohort study. *Am. J. Psychiatry*, **2008**, *165*(4), 515-523. http://dx.doi.org/10.1176/appi.ajp.2007.07061018

[8] Van Der Kooy, K.; Van Hout, H.; Marwijk, H.; Marten, H.; Stehouwer, C.; Beekman, A. Depression and the risk for cardiovascular diseases: systematic review and meta analysisv. *Intl. J. Geriatric Psychiatry*, **2007**, *22*(7), 613-626. http://dx.doi.org/10.1002/gps.1723

[9] Wood, S.K.; Woods, J.H. Corticotropin-releasing factor receptor-1: a therapeutic target for cardiac autonomic disturbances. *Expert Opin. Ther. Targets*, **2007**, *11*(11), 1401-1413. http://dx.doi.org/10.1517/14728222.11.11.1401

[10] Southwick, S.M.; Krystal, J.H.; Morgan, C.A.; Johnson, D.; Nagy, L.M.; Nicolaou, A.; Heninger, G.R.; Charney, D.S. Abnormal noradrenergic function in posttraumatic stress disorder. *Arch.Gen. Psychiatry*, **1993**, *50*(4), 266-274. PubMed ID: 8466387

[11] Almeida, D.M. Resilience and vulnerability to daily stressors assessed *via* diary methods. *Curr.Directions Psychol. Sci.*, 2005, *14*, 64-68. http://dx.doi.org/10.1111/j.0963-7214.2005.00336.x

[12] Albus, C. Psychological and social factors in coronary heart disease. *Ann Med*, 2010, *42*(7), 487-494. http://dx.doi.org/10.3109/07853890.2010.515605

[13] Bjorkqvist, K. Social defeat as a stressor in humans. *Physiol. Behav.*, **2001**, *73*(3), 435-442. http://dx.doi.org/10.1016/S0031-9384(01)00490-5

[14] Friedmann, E.; Thomas, S.A.; Liu, F.; Morton, P.G.; Chapa, D.; Gottlieb, S.S. Relationship of depression, anxiety, and social isolation to chronic heart failure outpatient mortality. *Am. Heart J*, **2006**, *152*(5), 940 e941-948. http://dx.doi.org/10.1016/j.ahj.2006.05.009

[15] Veenema, A.H.; Meijer, O.C.; de Kloet, E.R.; Koolhaas, J.M. Genetic selection for coping style predicts stressor susceptibility. *J. Neuroendocrinol.*, **2003**, *15*(3), 256-267. http://dx.doi.org/10.1046/j.1365-2826.2003.00986.x

[16] Billings, A.G.; Moos, R.H. Coping, stress, and social resources among adults with unipolar depression. *J. Pers Soc. Psychol.*, **1984**, *46*(4), 877-891. http://dx.doi.org/10.1037//0022-3514.46.4.877

[17] Folkman, S.; Lazarus, R.S. An analysis of coping in a middle-aged community sample. *J. Health Soc. Behav.*, **1980**, *21*(3), 219-239.

[18] Harburg, E.; Julius, S.; McGinn, N.F.; McLeod, J.; Hoobler, S.W. Personality Traits and Behavioral Patterns Associated with Systolic Blood Pressure Levels in College Males. *J. Chronic. Dis.*, 1964, *17*, 405-414.

[19] Julius, S. *The psychophysiology of borderline hypertension*. Raven: New York, **1981**, pp. 293-303.

[20] Esler, M.; Julius, S.; Zweifler, A.; Randall, O.; Harburg, E.; Gardiner, H.; DeQuattro, V. Mild high-renin essential hypertension. Neurogenic human hypertension? *N. Engl. J. Med.*, **1977**, *296*(8), 405-411. http://dx.doi.org/10.1056/NEJM197702242960801

[21] Southwick, S.M.; Vythilingam, M.; Charney, D.S. The psychobiology of depression and resilience to stress: implications for prevention and treatment. *Annu. Rev. Clin. Psychol.*, **2005**, *1*, 255-291. http://dx.doi.org/10.1146/annurev.clinpsy.1.102803.143948

[22] Wood, S.K.; Walker, H.E.; Valentino, R.J.; Bhatnagar, S. Individual differences in reactivity to social stress predict susceptibility and resilience to a depressive phenotype: role of corticotropin-releasing factor. *Endocrinology*, **2010**, *151*(4), 1795-1805. http://dx.doi.org/10.1210/en.2009-1026

[23] Koolhaas, J.M.; de Boer, S.F.; Buwalda, B.; van Reenen, K. Individual variation in coping with stress: a multidimensional approach of ultimate and proximate mechanisms. *Brain Behav. Evol.*, **2007**, *70*(4), 218-226. http://dx.doi.org/10.1159/000105485

[24] Miczek, K.A. A new test for aggression in rats without aversive stimulation: differential effects of d-amphetamine and cocaine. *Psychopharmacology (Berl)*, **1979**, *60*(3), 253-259. http://dx.doi.org/10.1007/BF00426664

[25] Wood, S.K.; McFadden, K.V.; Grigoriadis, D.; Bhatnagar, S.; Valentino, R.J. Depressive and cardiovascular disease comorbidity in a rat model of social stress: a putative role for corticotropin-releasing factor. *Psychopharmacology (Berl)*, **2012**, *222*(2), 325-336. http://dx.doi.org/10.1007/s00213-012-2648-6

[26] Carnevali, L.; Mastorci, F.; Graiani, G.; Razzoli, M.; Trombini, M.; Pico-Alfonso, M.A.; Arban, R.; Grippo, A.J.; Quaini, F.; Sgoifo, A. Social defeat and isolation induce clear signs of a depression-like state, but modest cardiac alterations in wild-type rats. *Physiol. Behav.*, **2012**, *106*(2), 142-150. http://dx.doi.org/10.1016/j.physbeh.2012.01.022

[27] Meerlo, P.; Sgoifo, A.; De Boer, S.F.; Koolhaas, J.M. Long-lasting consequences of a social conflict in rats: behavior during the interaction predicts subsequent changes in daily rhythms of heart rate, temperature, and activity. *Behav .Neurosci.*, **1999**, *113*(6), 1283-1290. http://dx.doi.org/10.1037//0735-7044.113.6.1283

[28] Walker, F.R.; Masters, L.M.; Dielenberg, R.A.; Day, T.A. Coping with defeat: acute glucocorticoid and forebrain responses to social defeat vary with defeat episode behaviour. *Neuroscience*, **2009**, *162*(2), 244-253. http://dx.doi.org/10.1016/j.neuroscience.2009.04.041

[29] Sgoifo, A.; de Boer, S.F.; Westenbroek, C.; Maes, F.W.; Beldhuis, H.; Suzuki, T.; Koolhaas, J.M. Incidence of arrhythmias and heart rate variability in wild-type rats exposed to social stress. *Am. J. Physiol.*, **1997**, *273*(4 Pt 2), H1754-1760. PubMed ID: 9362240

[30] Hawley, D.F.; Bardi, M.; Everette, A.M.; Higgins, T.J.; Tu, K.M.; Kinsley, C.H.; Lambert, K.G. Neurobiological constituents of active, passive, and variable coping strategies in rats: integration of regional brain neuropeptide Y levels and cardiovascular responses. *Stress*, **2010**, *13*(2), 172-183. http://dx.doi.org/10.3109/10253890903144621

[31] Fokkema, D.S.; Koolhaas, J.M.; van der Gugten, J. Individual characteristics of behavior, blood pressure, and adrenal hormones in colony rats. *Physiol. Behav.*, **1995**, *57*(5), 857-862. http://dx.doi.org/10.1016/0031-9384(94)00333-Z

[32] Vale, W.; Spiess, J.; Rivier, C.; Rivier, J. Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. *Science*, **1981**, *213*(4514), 1394-1397. http://dx.doi.org/10.1126/science.6267699

[33] Heinrichs, S.C.; Pich, E.M.; Miczek, K.A.; Britton, K.T.; Koob, G.F. Corticotropin-releasing factor antagonist reduces emotionality in socially defeated rats *via* direct neurotropic action. *Brain Res.*, **1992**, *581*(2), 190-197. PMID: 1327398

[34] Dunn, A.J.; Swiergiel, A.H. Effects of acute and chronic stressors and CRF in rat and mouse tests for depression. *Ann. N. Y. Acad. Sci.*, **2008**, *1148*, 118-126. http://dx.doi.org/10.1196/annals.1410.022

[35] Holsboer, F.; Ising, M. Central CRH system in depression and anxiety--evidence from clinical studies with CRH1 receptor antagonists. *Eur. J .Pharmacol.*, **2008**, *583*(2-3), 350-357. http://dx.doi.org/10.1016/j.ejphar.2007.12.032

[36] Ayala, A.R.; Pushkas, J.; Higley, J.D.; Ronsaville, D.; Gold, P.W.; Chrousos, G.P.; Pacak, K.; Calis, K.A.; Gerald, M.; Lindell, S.; Rice, K.C.; Cizza, G. Behavioral, adrenal, and sympathetic responses to long-term administration of an oral corticotropin-releasing hormone receptor antagonist in a primate stress paradigm. *J .Clin. Endocrinol. Metab.*, **2004**, *89*(11), 5729-5737. http://dx.doi.org/10.1210/jc.2003-032170

[37] Austin, M.C.; Janosky, J.E.; Murphy, H.A. Increased corticotropin-releasing hormone immunoreactivity in monoamine-containing pontine nuclei of depressed suicide men. *Mol. Psychiatry*, **2003**, *8*(3), 324-332. http://dx.doi.org/10.1038/sj.mp.4001250

[38] Bissette, G.; Klimek, V.; Pan, J.; Stockmeier, C.; Ordway, G. Elevated concentrations of CRF in the locus coeruleus of depressed subjects. *Neuropsychopharmacology*, **2003**, *28*(7), 1328-1335. http://dx.doi.org/10.1038/sj.npp.1300191

[39] Merali, Z.; Du, L.; Hrdina, P.; Palkovits, M.; Faludi, G.; Poulter, M.O.; Anisman, H. Dysregulation in the suicide brain: mRNA expression of corticotropin-releasing hormone receptors and GABA(A) receptor subunits in frontal cortical brain region. *J. Neurosci.*, **2004**, *24*(6), 1478-1485. http://dx.doi.org/10.1523/JNEUROSCI.4734-03.2004

[40] Boyson, C.O.; Miguel, T.T.; Quadros, I.M.; Debold, J.F.; Miczek, K.A. Prevention of social stress-escalated cocaine self-administration by CRF-R1 antagonist in the rat VTA. *Psychopharmacology (Berl)*, **2011**, *218*(1), 257-269. PMID: 21468623

[41] Nemeroff, C.B.; Widerlov, E.; Bissette, G.; Walleus, H.; Karlsson, I.; Eklund, K.; Kilts, C.D.; Loosen, P.T.; Vale, W. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. *Science*, **1984**, *226*(4680), 1342-1344. http://dx.doi.org/10.1126/science.6334362

[42] Makino, S.; Baker, R.A.; Smith, M.A.; Gold, P.W. Differential regulation of neuropeptide Y mRNA expression in the arcuate nucleus and locus coeruleus by stress and antidepressants. *J. Neuroendocrinol.*, **2000**, *12*(5), 387-395. http://dx.doi.org/10.1046/j.1365-2826.2000.00451.x

[43] Baker, R.A.; Herkenham, M. Arcuate nucleus neurons that project to the hypothalamic paraventricular nucleus: neuropeptidergic identity and consequences of adrenalectomy on mRNA levels in the rat. *J. Comp. Neurol.*, **1995**, *358*(4), 518-530. http://dx.doi.org/10.1002/cne.903580405

[44] Adrian, T.E.; Allen, J.M.; Bloom, S.R.; Ghatei, M.A.; Rossor, M.N.; Roberts, G.W.; Crow, T.J.; Tatemoto, K.; Polak, J.M. Neuropeptide Y distribution in human brain. *Nature*, **1983**, *306*(5943), 584-586. http://dx.doi.org/10.1038/306584a0

[45] Britton, K.T.; Akwa, Y.; Spina, M.G.; Koob, G.F. Neuropeptide Y blocks anxiogenic-like behavioral action of corticotropin-releasing factor in an operant conflict test and elevated plus maze. *Peptides*, **2000**, *21*(1), 37-44. http://dx.doi.org/10.1016/S0196-9781(99)00169-2

[46] Heilig, M.; Koob, G.F.; Ekman, R.; Britton, K.T. Corticotropin-releasing factor and neuropeptide Y: role in emotional integration. *Trends Neurosci.*, **1994**, *17*(2), 80-85. http://dx.doi.org/10.1016/0166-2236(94)90079-5

[47] Valentino, R.J.; Foote, S.L.; Aston-Jones, G. Corticotropin-releasing factor activates noradrenergic neurons of the locus coeruleus. *Brain Res.*, **1983**, *270*(2), 363-367. http://dx.doi.org/10.1016/0006-8993(83)90615-7

[48] Illes, P.; Finta, E.P.; Nieber, K. Neuropeptide Y potentiates *via* Y2-receptors the inhibitory effect of noradrenaline in rat locus coeruleus neurones. *Naunyn Schmiedebergs Arch. Pharmacol.*, **1993**, *348*(5), 546-548.

[49] Wong, M.L.; Kling, M.A.; Munson, P.J.; Listwak, S.; Licinio, J.; Prolo, P.; Karp, B.; McCutcheon, I.E.; Geracioti, T.D., Jr.; DeBellis, M.D.; Rice, K.C.; Goldstein, D.S.; Veldhuis, J.D.; Chrousos, G.P.; Oldfield, E.H.; McCann, S.M.; Gold, P.W. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. *Proc. Natl. Acad. Sci. U. S. A.*, **2000**, *97*(1), 325-330. http://dx.doi.org/10.1073/pnas.97.1.325

[50] Geracioti, T.D., Jr.; Baker, D.G.; Ekhator, N.N.; West, S.A.; Hill, K.K.; Bruce, A.B.; Schmidt, D.; Rounds-Kugler, B.; Yehuda, R.; Keck, P.E., Jr.; Kasckow, J.W. CSF norepinephrine concentrations in posttraumatic stress disorder. *Am. J. Psychiatry*, **2001**, *158*(8), 1227-1230.

[51] Cohen, H.; Liu, T.; Kozlovsky, N.; Kaplan, Z.; Zohar, J.; Mathe, A.A. The neuropeptide Y (NPY)-ergic system is associated with behavioral resilience to stress exposure in an animal model of post-traumatic stress disorder. *Neuropsychopharmacology*, **2012**, *37*(2), 350-363.

[52] Primeaux, S.D.; Wilson, S.P.; Cusick, M.C.; York, D.A.; Wilson, M.A. Effects of altered amygdalar neuropeptide Y expression on anxiety-related behaviors. *Neuropsychopharmacology*, **2005**, *30*(9), 1589-1597. PMID: 15770236

[53] Rasmusson, A.M.; Hauger, R.L.; Morgan, C.A.; Bremner, J.D.; Charney, D.S.; Southwick, S.M. Low baseline and yohimbine-stimulated plasma neuropeptide Y (NPY) levels in combat-related PTSD. *Biol. Psychiatry*, **2000**, *47*(6), 526-539. http://dx.doi.org/10.1016/S0006-3223(99)00185-7

[54] Klemfuss, H.; Southerland, S.; Britton, K.T. Cardiovascular actions of neuropeptide Y and social stress. *Peptides*, **1998**, *19*(1), 85-92. http://dx.doi.org/10.1016/S0196-9781(97)00266-0

[55] Morgan, C.A., 3rd; Wang, S.; Southwick, S.M.; Rasmusson, A.; Hazlett, G.; Hauger, R.L.; Charney, D.S. Plasma neuropeptide-Y concentrations in humans exposed to military survival training. *Biol. Psychiatry*, **2000**, *47*(10), 902-909. http://dx.doi.org/10.1016/S0006-3223(99)00239-5

[56] Chaijale, N.N.; Curtis, A.L.; Wood, S.K.; Zhang, X.Y.; Bhatnagar, S.; Reyes, B.A.; Van Bockstaele, E.J.; Valentino, R.J. Social Stress Engages Opioid Regulation of Locus Coeruleus Norepinephrine Neurons and Induces a State of Cellular and Physical Opiate Dependence. *Neuropsychopharmacology*, **2013**, *38*(10), 1833-43. PMID 23660707

[57] Mansour, A.; Fox, C.A.; Thompson, R.C.; Akil, H.; Watson, S.J. mu-Opioid receptor mRNA expression in the rat CNS: comparison to mu-receptor binding. *Brain Res.*, **1994**, *643*(1-2), 245-265. http://dx.doi.org/10.1016/0006-8993(94)90031-0

[58] Williams, J.T.; North, R.A. Opiate-receptor interactions on single locus coeruleus neurones. *Mol. Pharmacol.*, **1984**, *26*(3), 489-497. PubMed ID: 6092898

[59] Curtis, A.L.; Bello, N.T.; Valentino, R.J. Evidence for functional release of endogenous opioids in the locus ceruleus during stress termination. *J. Neurosci.*, **2001**, *21*(13), RC152. PMID 11406637

[60] West, C.H.; Ritchie, J.C.; Boss-Williams, K.A.; Weiss, J.M. Antidepressant drugs with differing pharmacological actions decrease activity of locus coeruleus neurons. *Int. J. Neuropsychopharmacol*, **2009**, *12*(5), 627-641. 10.1017/S1461145708009474

[61] Curtis, A.L.; Valentino, R.J. Corticotropin-releasing factor neurotransmission in locus coeruleus: a possible site of antidepressant action. *Brain Res. Bull*, **1994**, *35*(5-6), 581-587. http://dx.doi.org/10.1016/0361-9230(94)90172-4

[62] Elam, M.; Svensson, T.H.; Thoren, P. Differentiated cardiovascular afferent regulation of locus coeruleus neurons and sympathetic nerves. *Brain Res.*, **1985**, *358*(1-2), 77-84. http://dx.doi.org/10.1016/0006-8993(85)90950-3

[63] Yamaguchi, N.; Okada, S. Cyclooxygenase-1 and -2 in spinally projecting neurons are involved in CRF-induced sympathetic activation. *Auton. Neurosci.*, **2009**, *151*(2), 82-89. http://dx.doi.org/10.1016/j.autneu.2009.06.009

[64] Valentino, R.J.; Commons, K.G. Peptides that fine-tune the serotonin system. *Neuropeptides*, **2005**, *39*(1), 1-8. http://dx.doi.org/10.1016/j.npep.2004.09.005

[65] Waselus, M.; Nazzaro, C.; Valentino, R.J.; Van Bockstaele, E.J. Stress-induced redistribution of corticotropin-releasing factor receptor subtypes in the dorsal raphe nucleus. *Biol. Psychiatry*, **2009**, *66*(1), 76-83. http://dx.doi.org/10.1016/j.biopsych.2009.02.014

[66] Kirby, L.G.; Rice, K.C.; Valentino, R.J. Effects of corticotropin-releasing factor on neuronal activity in the serotonergic dorsal raphe nucleus. *Neuropsychopharmacology*, **2000**, *22*(2), 148-162. http://dx.doi.org/10.1016/S0893-133X(99)00093-7

[67] Price, M.L.; Curtis, A.L.; Kirby, L.G.; Valentino, R.J.; Lucki, I. Effects of corticotropin-releasing factor on brain serotonergic activity. *Neuropsychopharmacology*, **1998**, *18*(6), 492-502. http://dx.doi.org/10.1016/S0893-133X(97)00197-8

[68] Kirby, L.G.; Freeman-Daniels, E.; Lemos, J.C.; Nunan, J.D.; Lamy, C.; Akanwa, A.; Beck, S.G. Corticotropin-releasing factor increases GABA synaptic activity and induces inward current in 5-hydroxytryptamine dorsal raphe neurons. *J. Neurosci.*, **2008**, *28*(48), 12927-12937. http://dx.doi.org/10.1523/JNEUROSCI.2887-08.2008

[69] Price, M.L.; Lucki, I. Regulation of serotonin release in the lateral septum and striatum by corticotropin-releasing factor. *J. Neurosci.*, **2001**, *21*(8), 2833-2841. PubMed ID: 11306635

[70] Amat, J.; Tamblyn, J.P.; Paul, E.D.; Bland, S.T.; Amat, P.; Foster, A.C.; Watkins, L.R.; Maier, S.F. Microinjection of urocortin 2 into the dorsal raphe nucleus activates serotonergic neurons and increases extracellular serotonin in the basolateral amygdala. *Neuroscience*, **2004**, *129*(3), 509-519. http://dx.doi.org/10.1016/j.neuroscience.2004.07.052

[71] Lukkes, J.L.; Forster, G.L.; Renner, K.J.; Summers, C.H. Corticotropin-releasing factor 1 and 2 receptors in the dorsal raphe differentially affect serotonin release in the nucleus accumbens. *Eur. J. Pharmacol.,* **2008**, *578*(2-3), 185-193. http://dx.doi.org/10.1016/j.ejphar.2007.09.024

[72] Forster, G.L.; Pringle, R.B.; Mouw, N.J.; Vuong, S.M.; Watt, M.J.; Burke, A.R.; Lowry, C.A.; Summers, C.H.; Renner, K.J. Corticotropin-releasing factor in the dorsal raphe nucleus increases medial prefrontal cortical serotonin *via* type 2 receptors and median raphe nucleus activity. *Eur. J. Neurosci.*, **2008**, *28*(2), 299-310. http://dx.doi.org/10.1111/j.1460-9568.2008.06333.x

[73] Wood, S.K.; Zhang, X.Y.; Reyes, B.A.; Lee, C.S.; Van Bockstaele, E.J.; Valentino, R.J. Cellular adaptations of dorsal raphe serotonin neurons associated with the development of active coping in response to social stress. *Biol Psychiatry*, **2013**, *73*(11), 1087-1094. http://dx.doi.org/10.1016/j.biopsych.2013.01.026

[74] Nordstrom, P.; Asberg, M. Suicide risk and serotonin. *Int Clin Psychopharmacol*, **1992**, *6 Suppl 6*, 12-21. http://dx.doi.org/10.1097/00004850-199206006-00003

[75] Owens, M.J.; Nemeroff, C.B. Role of serotonin in the pathophysiology of depression: focus on the serotonin transporter. *Clin. Chem.*, **1994**, *40*(2), 288-295. PubMed ID: 7508830

[76] Watts, S.W.; Morrison, S.F.; Davis, R.P.; Barman, S.M. Serotonin and blood pressure regulation. *Pharmacol. Rev.*, **2012**, *64*(2), 359-388. http://dx.doi.org/10.1124/pr.111.004697

[77] Salim, S.; Asghar, M.; Chugh, G.; Taneja, M.; Xia, Z.; Saha, K. Oxidative stress: a potential recipe for anxiety, hypertension and insulin resistance. *Brain Res.*, **2010**, *1359*, 178-185. http://dx.doi.org/10.1016/j.brainres.2010.08.093

[78] Salim, S.; Asghar, M.; Taneja, M.; Hovatta, I.; Chugh, G.; Vollert, C.; Vu, A. Potential contribution of oxidative stress and inflammation to anxiety and hypertension. *Brain Res.*, **2011**, *1404*, 63-71. http://dx.doi.org/10.1016/j.brainres.2011.06.024

[79] de Oliveira, M.R.; Silvestrin, R.B.; Mello, E.S.T.; Moreira, J.C. Oxidative stress in the hippocampus, anxiety-like behavior and decreased locomotory and exploratory activity of adult rats: effects of sub acute vitamin A supplementation at therapeutic doses. *Neurotoxicology*, **2007**, *28*(6), 1191-1199. http://dx.doi.org/10.1016/j.neuro.2007.07.008

[80] Leonard, B.; Maes, M. Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci. Biobehav. Rev.*, **2012**, *36*(2), 764-785. http://dx.doi.org/10.1016/j.neubiorev.2011.12.005

[81] Patki, G.; Solanki, N.; Atrooz, F.; Allam, F.; Salim, S. Depression, anxiety-like behavior and memory impairment are associated with increased oxidative stress and inflammation in a rat model of social stress. *Brain Res.*, **2013**, *In Press*.

[82] Frommberger, U.H.; Bauer, J.; Haselbauer, P.; Fraulin, A.; Riemann, D.; Berger, M. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. *Eur. Arch. Psychiatry Clin. Neurosci.*, **1997**, *247*(4), 228-233. PMID: 9332905

[83] Fagundes, C.P.; Glaser, R.; Hwang, B.S.; Malarkey, W.B.; Kiecolt-Glaser, J.K. Depressive symptoms enhance stress-induced inflammatory responses. *Brain Behav. Immun.*, **2013**, *31*, 172-176. PMID: 22634107

[84] Pace, T.W.; Mletzko, T.C.; Alagbe, O.; Musselman, D.L.; Nemeroff, C.B.; Miller, A.H.; Heim, C.M. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am. J. Psychiatry*, **2006**, *163*(9), 1630-1633. PMID:16946190

[85] Derry, H.M.; Fagundes, C.P.; Andridge, R.; Glaser, R.; Malarkey, W.B.; Kiecolt-Glaser, J.K. Lower subjective social status exaggerates interleukin-6 responses to a laboratory stressor. *Psychoneuroendocrinology*, **2013**, *38*(11), 2676-2685.

[86] Chourbaji, S.; Urani, A.; Inta, I.; Sanchis-Segura, C.; Brandwein, C.; Zink, M.; Schwaninger, M.; Gass, P. IL-6 knockout mice exhibit resistance to stress-induced development of depression-like behaviors. *Neurobiol. Dis.*, **2006**, *23*(3), 587-594. PMID: 16843000

[87] Bartolomucci, A.; Palanza, P.; Parmigiani, S.; Pederzani, T.; Merlot, E.; Neveu, P.J.; Dantzer, R. Chronic psychosocial stress down-regulates central cytokines mRNA. *Brain Res. Bull.*, **2003**, *62*(3), 173-178. http://dx.doi.org/10.1016/j.brainresbull.2003.09.009

[88] Maes, M.; Yirmyia, R.; Noraberg, J.; Brene, S.; Hibbeln, J.; Perini, G.; Kubera, M.; Bob, P.; Lerer, B.; Maj, M. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metab. Brain Dis.*, **2009**, *24*(1), 27-53. http://dx.doi.org/10.1007/s11011-008-9118-1

[89] Dantzer, R.; O'Connor, J.C.; Freund, G.G.; Johnson, R.W.; Kelley, K.W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.*, **2008**, *9*(1), 46-56. : http://dx.doi.org/10.1038/nrn2297

[90] Rawdin, B.J.; Mellon, S.H.; Dhabhar, F.S.; Epel, E.S.; Puterman, E.; Su, Y.; Burke, H.M.; Reus, V.I.; Rosser, R.; Hamilton, S.P.; Nelson, J.C.; Wolkowitz, O.M. Dysregulated relationship of inflammation and oxidative stress in major depression. *Brain Behav. Immun.*, **2013**, *31*, 143-152. http://dx.doi.org/10.1016/j.bbi.2012.11.011

Received: August 19, 2013 Revised: September 02, 2013 Accepted: November 02, 2013