Review

Cytokines, prostaglandins and nitric oxide in the regulation of stress-response systems

Anna Gądek-Michalska, Joanna Tadeusz, Paulina Rachwalska, Jan Bugajski

Department of Physiology, Institute of Pharmacology, Polish Academy of Sciences, Smętna 12, PL 31-343 Kraków, Poland

Correspondence: Anna Gądek-Michalska, e-mail: gadek@if-pan.krakow.pl

Abstract:

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is accepted as one of the fundamental biological mechanisms that underlie major depression. This hyperactivity is caused by diminished feedback inhibition of glucocorticoid (GC)-induced reduction of HPA axis signaling and increased corticotrophin-releasing hormone (CRH) secretion from the hypothalamic paraventricular nucleus (PVN) and extra-hypothalamic neurons. During chronic stress-induced inhibition of systemic feedback, cytosolic glucocorticoid receptor (GR) levels were significantly changed in the prefrontal cortex (PFC) and hippocampus, both structures known to be deeply involved in the pathogenesis of depression.

Cytokines secreted by both immune and non-immune cells can markedly affect neurotransmission within regulatory brain circuits related to the expression of emotions; cytokines may also induce hormonal changes similar to those observed following exposure to stress. Proinflammatory cytokines, including interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are implicated in the etiologies of clinical depression and anxiety disorders. Prolonged stress responses and cytokines impair neuronal plasticity and stimulation of neurotransmission. Exposure to acute stress and IL-1β markedly increased IL-1β levels in the PFC, hippocampus and hypothalamus, as well as overall HPA axis activity. Repeated stress sensitized the HPA axis response to IL-1β.

Inflammatory responses in the brain contribute to cellular damage associated with neuropsychiatric diseases related to stress. Physical, psychological or combined-stress conditions evoke a proinflammatory response in the brain and other systems, characterized by a complex release of several inflammatory mediators including cytokines, prostanoids, nitric oxide (NO) and transcription factors.

Induced CRH release involves IL-1, IL-6 and TNF-α, for stimulation adrenocorticotropic hormone (ACTH) release from the anterior pituitary. NO also participates in signal transduction pathways that result in the release of corticosterone from the adrenal gland. NO participates in multiple interactions between neuroendocrine and neuroimmune systems in physiological and pathological processes. Neuronal NO synthase (nNOS) modulates learning and memory and is involved in development of neuropsychiatric diseases, including depression. Nitric oxide generated in response to stress exposure is associated with depression-like and anxiety-like behaviors.

In the central nervous system (CNS), prostaglandins (PG) generated by the cyclooxygenase (COX) enzyme are involved in the regulation of HPA axis activity. Prior exposure to chronic stress alters constitutive (COX-1) and inducible (COX-2) cyclooxygenase responses to homotypic stress differently in the PFC, hippocampus and hypothalamus. Both PG and NO generated within the PVN participate in this modulation. Acute stress affects the functionality of COX/PG and NOS/NO systems in brain structures. The complex responses of central and peripheral pathways to acute and chronic stress involve cytokines, NO and PG systems that regulate and turn off responses that would be potentially harmful for cellular homeostasis and overall health.

Key words:

Depression, hypothalamic-pituitary-adrenal axis, stress, interleukin-1β, neuronal nitric oxide synthase, inducible nitric oxide synthase, prostaglandins, constitutive cyclooxygenase, inducible cyclooxygenase

Hypothalamic-pituitary-adrenal (HPA) axis dysfunction and depression

Dysregulation of the neuroimmune-endocrine system is accepted as one of the fundamental biological mechanisms that underlie psychiatric disorders [17, 28, 32]. Earlier investigations on the pathophysiology of depression have provided strong evidence that depressed patients manifest HPA axis hyperactivity [1]. Differential adrenocortical activity between depressed patients and normal subjects is regarded as the most reproducible finding in all of biological psychiatry. An additional established finding is that patients who manifest the most severe depression demonstrate more severe HPA axis hyperactivity. Extensive investigation over the last four decades has confirmed that hyperactivity of the HPA axis is one of the most reliable biological findings in major depression [20, 21]. In depressed patients, increased numbers of neurons expressing CRH and increased messenger ribonucleic acid (mRNA) levels of CRH receptors in the PVN were found at autopsy, suggesting elevated *pre-mortem* CRH cell activity. The HPA axis hyperactivity observed in depressive illness is accompanied by diminished glucocorticoid-related feedback inhibition of the HPA axis. Increased GC resistance may also be related to hypercortisolism, a commonly-occurring condition in patients suffering from stress-related illnesses such as depression. The availability of glucocorticoids in systemic circulation may be decreased up to 90% by corticosteroid-binding globulin and other local factors that reduce GC concentrations available to the cell, thus contributing to a state of GC resistance [21]. Disruption of the GC-mediated negative feedback system is observed in approximately one half of human depressives [23]. Chronic stress can precipitate or exacerbate neuropsychiatric disorders. Altered glucocorticoid receptors (GRs) in stress-sensitive structures of the brain are involved in chronic stress-mediated inhibition of feedback. Cytosolic GR levels were decreased in the PFC and increased in the hippocampus, but GR levels were not markedly changed in the hypothalamus. These findings support the theory that significant dysfunction of cellular signaling pathways in the PFC and the hippocampus is critical to the pathogenesis of depression.

Chronic psychogenic stressors can induce persistent activation of the neuroendocrine HPA axis and result in cellular alteration of brain regions that then are sensitive to subsequent stressors present in various psychiatric and somatic disorders. Both high doses of exogenous steroids and high concentrations of endogenous GCs may evoke mood disorders or depressive symptomatology in some individuals [21]. However, the mechanisms of these effects are currently unknown. In depressed individuals, CRH is hypersecreted from hypothalamic PVN and from extrahypothalamic neurons, which leads to hyperactivity of the HPA axis in the presence of reduced feedback inhibition by endogenous glucocorticoids. This increased CRH neuronal activity may also mediate certain behavioral symptoms and psychomotor changes experienced during depression [1].

HPA axis hyperactivity in depression is not suppressed by pharmacological stimulation of the GR or the mineralocorticoid receptor (MR) with the synthetic glucocorticoid dexamethasone, a potent feedback inhibitor of the HPA axis in healthy subjects [28].

Stress increases brain glucocorticoid levels and the number of GR receptors in brain structures. The prefrontal cortex region contains high level of GRs that modulate HPA function. The PFC is hypothesized to mediate a stressor-specific inhibition of HPA function. Lesions of the medial prefrontal cortex (mPFC) increase ACTH and corticosterone secretions locally. During stress exposure, when corticosterone level is increased considerably, GRs are occupied by corticosterone and suppress stress-induced hyperactivity of the HPA axis in the PVN, anterior pituitary and hippocampus. Thus, the adaptive function of the HPA axis

is critically dependent on glucocorticoid feedback mechanisms to dampen the stressor-induced activation of the HPA axis and to shut off further glucocorticoid secretion [3, 7]. Disruption of the glucocorticoid negative feedback system in animals by chronic stress exposure may be a result of a downregulation of GRs in several stress-sensitive brain regions.

We compared the dynamic changes in plasma ACTH and corticosterone levels with alterations in GR and MR content in brain structures involved in mediating the stress response, including the PFC, hippocampus and hypothalamus. We found that the buffering effect of repeated stress exposure depends on the length of the period of habituation to stress and is accompanied by parallel decreases in CRH mRNA levels in PVN and GC receptor gene transcription in the hippocampus CA-1 region. Chronic stress has been shown to significantly down-regulate MR and GR mRNA expression in the PVN to 60% of control values [30]. GCs exert inhibitory feedback at the hypothalamus and pituitary gland to inhibit the synthesis and secretion of CRH and proopiomelanocortin (POMC) or ACTH. In addition, hippocampal tissue with a high density of GRs decreases PVN and HPA activity [21, 32]. In recent years, the immune system has been implicated in chronic psychiatric disorders [9, 19, 26, 31]. Acute phase proteins and several proinflammatory cytokines, including IL-1β, IL-6 and TNF-α along with other general inflammatory indicators, are high in the serum of depressed patients [16]. Acute and chronic stressors dysregulate or impair certain functions of innate immunity. Clinical depression is also associated with some immune disturbances such as increased levels of PGs, corticoid hormones, and positive acute phase proteins [25]. Recently, the possibility that anti-inflammatory agents could provide an additive therapeutic action when combined with traditional anti-depressants was suggested. Cytokines may also markedly affect neurotransmission within regulatory brain circuits for emotion [2] and induce hormonal changes similar to those observed following exposure to stressors. Recent evidence further implicates cytokines in the etiologies of clinical depression and anxiety disorders. Cytokines are elevated in severe depressive illness and following stressor exposure. Stressors and cytokines share an ability to impair neuronal plasticity and stimulation of neurotransmission. Depressive illness may be regarded as a disorder of neuroplasticity and as one of neurochemical dysfunction, and cytokines may mediate

both of these mechanisms of illness. However, it is likely that cytokines are important for only a subset of depressive symptoms [17]. Cytokines often evoke effects resembling physical sickness, which may be present in some forms of depression. Therefore, cytokines may comprise one set of potentially very important triggers acting together with psychosocial stimuli to manifest depression. However, in prevalent experimental models of depression, the intimate relationship between stressor exposure and the onset of illness have not been demonstrated.

Cytokine-induced stimulation of the HPA axis under basal and stress conditions

Cytokines, generally secreted by cells of the immune system, may also be synthesized and secreted by non-immune cells in order to signal neuroimmune cells. Interleukin-1β is one of the major proinflammatory cytokines involved in the regulation of HPA axis activity in the brain [15]. IL-1β is expressed in all components of the HPA axis, affects the secretion of CRH from the hypothalamus, ACTH from the pituitary and glucocorticoids from the adrenal cortex. Furthermore, IL-1β may also directly induce both ACTH secretion from the pituitary *via* IL-1 type I receptors (IL-1RI) and the secretion of corticosterone from the adrenals [24]. In addition to circulating cytokines, which may act at all of these HPA axis regulatory levels, cytokines are also generated in the brain, the anterior pituitary and the adrenal cortex. Cytokine receptors have been detected in all tissues and regulatory levels of the HPA axis, and therefore each center of HPA axis activity can function as an integration point for immune and neuroendocrine signals.

Peripheral administration of IL-1β activates the HPA axis. Although the blood-brain barrier (BBB) presents a physical barrier to the cytokine-CNS interaction, cytokines may enter the brain *via* the fenestrated endothelium of the circumventricular organs (CVOs). This transport occurs *via* either the induction of cytokine release from the cells of the BBB into the brain parenchyma or by transport across the BBB by infiltrating leukocytes. Cytokines may also act peripherally by affecting the CNS *via* neuroadrenergic, serotonergic, dopaminergic or γ-aminobutyric acid (GABA)-ergic pathways and stimulation of the ascending visceral peripheral neural pathways, mainly

vagus nerves that convey signals to endocrine neurons in the PVN and supraoptic nuclei (SON) of the hypothalamus. Viscerosensory inputs to the CRH neurons within the PVN are preferentially noradrenergic. In the hypothalamus the noradrenergic innervation of the paraventricular nuclei mediate IL-1 activation of the HPA axis. Cytokines normally produced by peripheral immune cells are also generated by CNS glial cells. Neuroimmune interactions involving peripheral and glial-derived cytokines play an important role in mediating depression [16, 17, 26].

We found that systemic administration of IL-1β increased plasma levels of ACTH and corticosterone considerably. Interleukin-1β administered *ip* may stimulate the HPA axis by direct activation of the median eminence outside of the BBB, resulting in the release of CRH from PVN neurons, the release of ACTH from anterior pituitary adrenocorticotroph cells, and direct stimulation of the adrenal cortex to secrete corticosterone. Systemically administered IL-1β also induced further IL-1β expression; this may have been the result of an autocrine signaling loop that influenced the adrenal response. This autocrine signaling loop may explain the dissociation between plasma ACTH and corticosterone levels. The strong inhibition of these IL-1β-induced stimulations by *ip* pretreatment with an IL-1 receptor antagonist (IL-1ra) indicates that these effects depend, at least partially, on selective IL-1 receptor stimulation [12]. Under basal conditions, exogenous IL-1 may reach central cytokine receptors in brain structures involved in HPA axis regulation. One hour after *ip* administration, IL-1β content was significantly increased in the prefrontal cortex and hippocampus and moderately increased in the hypothalamus. These increased levels markedly declined 2 h after IL-1β administration and were parallel but considerably lower than the changes in plasma IL-1β levels. The rate of change in IL-1β content in brain structures involved in HPA axis regulation appeared structure- and time-dependent. The changes in plasma IL-1β levels were generally parallel with plasma ACTH and corticosterone levels, suggesting that IL-1β both in the brain and in plasma is involved in the regulation of HPA axis activity under basal conditions in non-stressed rats. Increased plasma IL-1β levels preceded a similar enhancement of ACTH and corticosterone secretion. An IL-1β receptor antagonist abolished the increased ACTH and corticosterone concentrations in response to exogenous IL-1β, indicating that these effects were IL-1 receptor-selective.

Acute restraint stress alone markedly increased IL-1β levels in brain stress-sensitive structures immediately after termination of the stress. Prior exposure to repeated restraint enhanced the homotypic stress-induced increase in IL-1β levels in prefrontal cortex, hippocampus, hypothalamus and plasma.

Prior stress sensitized ACTH and corticosterone responses to *ip* IL-1β exposure. Thus, acute stress demonstrated a modulatory role in the IL-1β-induced HPA axis activation under basal and stress conditions [10, 11, 22].

Multiple distinct stressors induced different IL-1β and HPA axis responses [6]. An IL-1β antagonist abolished the increase in ACTH and corticosterone responses to repeated stress for 3 days and reduced the enhancement of plasma corticosterone levels induced by homotypic stress conditions [3]. This suggests that central and peripheral mechanisms modulating the stress-induced HPA axis response require IL-1β receptors. Circulating cytokines and their mRNA expression within the prefrontal cortex and hippocampus varied by the stressor experience and by the specific cytokine. The impact of exposure to stressors varied with the nature of the stress challenge [14].

Brain NO/NOS systems in IL-1β- and stress-induced stimulation of the HPA axis

Nitric oxide (NO) is a signaling molecule for various cell types and systems, and also serves as a neurotransmitter in the brain. Under physiological conditions, neuronal NO synthase (nNOS) is constitutively expressed, and it constitutes the major isoenzyme of NOS in the brain. Inducible NO synthase (iNOS) is undetectable under basal conditions, and it is upregulated in response to various stimuli such as inflammatory cytokines and stress [27]. NO generated by iNOS in the brain is involved in central-induced elevation of plasma CRH, but it is not clear whether nNOS plays a role in these CRH-induced elevations. nNOS is highly expressed by cells of the hypothalamic PVN, the convergence point for the sympathoadrenal system, the HPA axis and the hypothalamo-neurohypophyseal system [29]. These structures regulate neuroendocrine stress responses. NO generated by nNOS plays a significant role in modulating the activity of these systems under acute stressor exposure. NOS constitutive forms are found in PVN, CRH and

vasopressin (AVP) neurons, as well as in direct and indirect afferences to the PVN found in the hippocampus, the dorsomedial lateral part of the hypothalamus and the amygdala [23].

Interleukin-1β is the major cytokine involved in activation of the HPA axis and modulates both central and peripheral components that regulate HPA activity [11]. NO generated by nNOS and iNOS in brain structures is involved in HPA axis regulation. IL-1β-induced transient stimulation of the HPA axis is parallel in time and magnitude to the respective changes of nNOS levels in the hypothalamus and prefrontal cortex, the brain structures involved in regulation of HPA axis activity [13].

Hippocampal damage increases PVN, CRH and AVP gene expression and the extent of PVN neural activation after stress, suggesting that hippocampal inhibition of the HPA axis is mediated *via* the PVN. Medial PFC is implicated in HPA axis inhibition. Lesions of prelimbic and anterior cingulated subregions of the mPFC increase ACTH and corticosterone secretions and PVN cFos mRNA induction after restraint stress. The role of corticosterone in HPA integration may depend on the subregion and hemisphere. IL-1β and NO are involved in noradrenaline induced CRH release. Application of N$^\omega$-nitro-L-arginine (L-NNA), a fairly selective inhibitor of neuronal nitric oxide synthase, attenuated IL-1β-induced CRH release, indicating that NO mediates this secretion. IL-1β plays a significant role in noradrenaline-induced CRH release, and the neuroendocrine response in the PVN may depend on local NO action. The stimulation of HPA axis activity by *ip* administration of IL-1β may be mediated by NO generated by nNOS and iNOS in the prefrontal cortex, hypothalamus and hippocampus.

The stimulatory effect of IL-1β on nNOS and iNOS activity was mostly prevented by prior administration of an IL-1 receptor antagonist, which suggests that the effects of nNOS and iNOS were IL-1 receptor-dependent. The general NOS inhibitor, N$^\omega$-nitro-L-arginine methyl ester (L-NAME), considerably reduced the ACTH and corticosterone response to IL-1β in rats. Repeated stress markedly increased IL-1β generation in brain structures involved in HPA axis activity. Interleukin-1β induced the highest and most persistent increase in nNOS protein levels in the hypothalamus, a slightly diminished stimulatory effect in the prefrontal cortex and a progressive increase in the hippocampus, which may have been related to the decreased and delayed action of neurons of the

hippocampus on HPA axis activity [11, 13]. In agreement with our data, NO donor 3-morpholino-syndomine (SIN-1) microinfused into the PVN, the site of the majority of the CRH neurons regulating HPA axis activity, significantly increased plasma ACTH levels.

Microinfusion of SIN-1 into the hippocampus also increased plasma ACTH levels to a smaller extent in a delayed manner when compared to responses following PVN treatment. IL-1β exposure considerably increased nNOS levels in the prefrontal cortex early after administration. Increased NO levels in the prefrontal cortex was parallel with, and may be involved in, enhanced HPA axis activity. These data indicate that NO may stimulate the HPA axis when applied to different brain regions.

Our data suggest that the IL-1β -induced central action of NO stimulates the HPA axis. They also provide information regarding the role of the hypothalamus and prefrontal cortex in modulating the activity of NOS on HPA activity during stimulation with systemic IL-1β administration [11].

NO functions like a neurotransmitter with the ability to spread extremely rapidly through cell membranes in the mammalian CNS, enabling NO to operate much more effectively than other transmitters. Neuronal NO synthase is highly expressed by cells of the hypothalamic paraventricular nuclei, which contained high levels of nNOS mRNA and protein. Brain nNOS is present in both particulate and soluble forms, and the differential subcellular localization of nNOS may contribute to its diverse functions [33, 34]. Neuronal NOS is involved in a variety of synaptic events and may modulate physiological function and a number of human disease states. In neurons, nNOS is located mainly at the post-synaptic terminal. Due to its ability to freely cross cell membranes, NO can act in both autocrine and paracrine pathways involving targets that are relatively distant from its site of origin. The endothelial and neuronal NO synthase regulates formation of small, basal amounts of NO. In the PVN of the hypothalamus, NO inhibits sympathetic outflow *via* increased GABA release. NO potentiates GABA-ergic synaptic inputs to spinally-projecting PVN neurons through a cyclic guanosine monophosphate (cGMP) protein kinase G pathway. Further, central nNOS is involved in restraint stress-induced responses. In experimental conditions, NO can either enhance or suppress the secretion of a number of cytokines including IL-1 [18].

Under stressful conditions, NOS isoenzymes mediate central, CRH-induced sympathetic activation and may affect HPA axis activity. The general stress response involves increased NO production due to induced expression of iNOS by stress mediators, and thus iNOS and NO are implicated in the pathophysiology of stress-induced inflammation. IL-1β may mediate some of the behavioral responses, that occur during stress, including depressive-like behaviors, whereas NO synthesized in response to stress exposure may cause depression-like and anxiety-like behaviors in rats. In stressed mice, antidepressant-like activity may be related to the inhibition of plasma iNOS activity. In the stress axis, NOS subtypes, particularly nNOS, are present in the hippocampus, pituitary and adrenal gland [24]. The IL-1β-induced transient stimulation of HPA axis activity was parallel in time and magnitude to respective changes in NOS content in the prefrontal cortex and hypothalamus, the brain structures involved in regulation of HPA axis activity.

Involvement of brain PG/COX systems in IL-1β- and stress-activation of the HPA axis

Prostaglandins are products of the cyclooxygenase (COX) pathway of arachidonic acid metabolism. COX-1 is constitutively expressed in a variety of cells and tissues. The other isoform, COX-2, is the product of an immediate early response gene in inflammatory cells. The expression of COX-2 is induced by endotoxins or cytokines including IL-1 and TNF-α. In the brain, COX-2 may be expressed constitutively and is regarded as the predominant isoform; its basal expression appears to be regulated by natural synaptic activity in the developing and adult brain. In the CNS, prostaglandins generated by COX-1 and COX-2 cyclooxygenases are involved in the regulation of HPA axis activity by neurotransmitters and neuropeptides. COX-1 and COX-2 mediate, to different extents, the secretion of ACTH and corticosterone in response to stimulation by cholinergic and adrenergic transmitters. In the CNS, prostaglandins generated by cyclooxygenases are involved in the regulation of HPA axis activity under basal and stress conditions. In brain structures, COX-1 and COX-2 levels change in response to homotypic, acute restraint stress in rats that were previously repeatedly restrained. We found that a prior restraint for 3 days decreased the homotypic stress-enhanced COX-1 levels, but markedly increased acute stress-induced COX-2 levels in the hippocampus. COX-1 levels in the hippocampus and hypothalamus remained elevated. Repeated stress for 3 days desensitized the HPA axis response to acute homotypic stress. This suggests the involvement of brain COX-1 and COX-2 in the HPA axis response under stress conditions. There are many pathways by which circulating IL-1β may interact with vascular and perivascular IL-1 type I receptor signals in the brain. In addition to iNOS induction, vascular IL-1RI activation causes induction of COX-2, resulting in PG synthesis. Brain vasculature within the PVN may induce the generation of PG or NO, which would modulate the effects of IL-1 on PVN function during stress.

General responses to stress involve expression of the inducible isoform of NOS and COX by specific stress mediators in different brain regions. Under physiological conditions, COX-1 is mainly expressed in microglia and perivascular cells, and COX-2 is localized in post-synaptic dendrites and excitatory terminals [4], particularly in the cortex, hippocampus and amygdale, with both neuronal and vascular associations. Prostaglandins generated by COX-2 and NO synthesized by iNOS cooperate during stress-induced HPA axis responses. PGE_2 produced by various cell types may integrate various stress stimuli, acting *via* PGE receptor subtypes EP1 and EP3 that are involved in ACTH secretion [8].

Acute restraint stress significantly increased COX-1 levels in the prefrontal cortex and hypothalamus. In the hippocampus, changes in COX-1 levels were moderate and not significant. COX-2 levels in the prefrontal cortex were slightly decreased when compared with non-stressed rats, whereas COX-2 levels in the hippocampus remained elevated. In the hypothalamus, COX-2 levels were markedly increased after termination of restraint stress. Immediately after termination of acute restraint stress, nNOS and iNOS levels in brain structures were significantly changed. Acute stress may affect the function of COX/PG and NOS/NO signaling systems in brain structures involved in the regulation of HPA axis [5].

Concluding remarks

Dysregulation of the neuroimmune-endocrine system is accepted as one of the fundamental biological mechanisms that underlie psychiatric disorders.

Hyperactivity of the HPA axis is one of the most reliable biological findings in patients suffering from major depression. This hyperactivity is caused by diminished feedback inhibition of GC-induced reduction of HPA axis signaling in healthy individuals, as well as increased CRH secretion from the hypothalamic PVN and extrahypothalamic neurons. During chronic stress-induced inhibition of feedback, cytosolic GR levels were significantly changed in the PFC and hippocampus, the structures significantly involved in the pathogenesis of depression.

Cytokines secreted by immune and non-immune cells can markedly affect neurotransmission within regulatory brain circuits for emotion responses and induce hormonal changes similar to those observed following stressor exposure. Proinflammatory cytokines, including IL-1β, IL-6 and TNF-α, are implicated in the etiologies of clinical depression and anxiety disorders.

Exposure to stress and cytokine responses may impair neuronal plasticity and stimulation of neurotransmission. Administration of exogenous IL-1β significantly enhanced IL-1β levels in the PFC and hippocampus, and further increased HPA axis activity. Likewise, acute stress markedly increased IL-1β levels in the PFC, hippocampus and hypothalamus. Repeated stress sensitized the HPA axis response to administration of exogenous IL-1β.

Inflammatory responses in the brain contribute to cellular damage associated with stress-induced neuropsychiatric diseases. Physical, psychological or combined stress exposures all evoke proinflammatory responses in the brain and other systems, which are characterized by a complex release of several inflammatory mediators including cytokines, prostanoids and transcription factors. In response to stress, anti-inflammatory mechanisms are also activated in brain.

The participation of NO in pathological processes is well established. The stimulated release of CRH involves NO and IL-1, and the stimulated release of ACTH from the anterior pituitary involves NO, IL-6 and TNF-α. NO also participates in signal transduction pathways in physiological processes including corticosterone release from the adrenal gland. NO participates widely in interactions between neuroendocrine and neuroimmune systems in physiological and pathological processes. Neuronal NOS is implicated in modulating learning, memory and neurogenesis, and it is also involved in the pathogenesis of a number of human diseases, including depression. nNOS is highly expressed by cells of the hypothalamic PVN, the convergence point for the sympatho-adrenal system, the HPA axis and the hypothalamo-hypophyseal regulatory system. NO generated in response to stress exposure causes depression-like and anxiety-like behaviors.

In the CNS, prostaglandins generated by COX are involved in the regulation of HPA axis activity under basal and stress conditions. Prior exposure to chronic stress alters COX-1 and COX-2 responses to homotypic acute stress, that differ in the PFC, hippocampus and hypothalamus. Both PG and NO generated within the PVN participate in this modulation. Acute stress may affect the function of COX/PG and NOS/NO systems in brain structures. The complex responses of central and peripheral pathways to acute and chronic stress involve cytokines, NO and PG systems that regulate and turn off responses that could be potentially harmful for cellular homeostasis and human health.

References:

1. Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB: The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol, 1999, 160, 1–12.
2. Arnsten AFT: Stress signalling pathways that impair prefrontal cortex structure and function. Nat Rev Neurosci, 2009, 10, 410–420.
3. Belda X, Rotllant D, Fuentes S, Delgado R, Nadal R, Armario A: Exposure to severe stressors causes long-lasting dysregulation of resting and stress-induced activation of the hypothalamic-pituitary adrenal axis. Ann N Y Acad Sci, 2008, 1148, 165–173.
4. Choi SH, Aid S, Bosetti F: The distinct roles of cyclooxygenase-1 and -2 in neuroinflammation: implications for translational research. Trends Pharmacol Sci, 2009, 30, 174–181.
5. Crangolini AB, Caruso C, Lasaga M, Scimonelli TN: α-MSH and γ-MSH modulate early release of hypothalamic PGE2 and NO induced by IL-1β differently. Neurosci Lett, 2006, 409, 168–172.
6. Deak T, Bordner KA, McElderry NK, Barnum CJ, Blandino P Jr, Deak MM, Tammariello SP: Stress-induced increases in hypothalamic IL-1: a systematic analysis of multiple stressor paradigms. Brain Res Bull, 2005, 64, 541–556.
7. Fuchs E, Flugge G: Chronic social stress effects on limbic brain structures. Physiol Behav, 2003, 79, 417–427.

8. Furuyashiki T, Narumiya S: Roles of prostaglandin E receptors in stress responses. Curr Opin Pharmacol, 2009, 9, 31–38.

9. García-Bueno B, Caso JR, Leza JC: Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. Neurosci Biobehav Rev, 2008, 32, 1136–1151.

10. Gądek-Michalska A, Bugajski J: Interleukin-1 (IL-1) in stress-induced activation of limbic-hypothalamic-pituitary adrenal axis. Pharmacol Rep, 2010, 62, 969–982.

11. Gądek-Michalska A,Tadeusz J, Rachwalska P, Spyrka J, Bugajski J: Brain nitric oxide synthases in the interleukin-1β-induced activation of hypothalamic-pituitary-adrenal axis. Pharmacol Rep, 2012, 64, 1455–1465.

12. Gądek-Michalska A, Tadeusz J, Rachwalska P, Spyrka J, Bugajski J: Effect of prior stress on interleukin-1β and HPA axis responses to acute stress. Pharmacol Rep, 2011, 63, 1393–1403.

13. Gądek-Michalska A, Tadeusz J, Rachwalska P, Spyrka J, Bugajski J: Effect of repeated restraint on homotypic stress-induced nitric oxide synthases expression in brain structures regulating HPA axis. Pharmacol Rep, 2012, 64, 1381–1390.

14. Gibb J, Hayley S, Poulter MO, Anisman H: Effects of stressors and immune activating agents on peripheral and central cytokines in mouse strains that differ in stressor responsivity. Brain Behav Immun, 2011, 25, 468–482.

15. Goshen I, Yirmiya R: Interleukin-1 (IL-1): a central regulator of stress responses. Front Neuroendocrinol, 2009, 30, 30–45.

16. Hayley S: Toward an anti-inflammatory strategy for depression. Front Behav Neurosci, 2011, 5, 1–7.

17. Hayley S, Poulter MO, Merali Z, Anisman H: The pathogenesis of clinical depression: stressor- and cytokine-induced alterations of neuroplasticity. Neuroscience, 2005, 135, 659–678.

18. Levy BH, Tasker JG: Synaptic regulation of the hypothalamic-pituitary-adrenal axis and its modulation by glucocorticoids and stress. Front Cell Neurosci, 2012, 6, 1–13.

19. Licinio J, Mastronardi C, Wong ML: Pharmacogenomics of neuroimmune interactions in human psychiatric disorders. Exp Physiol, 2007, 92, 807–811.

20. Licinio J, Wong ML: The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. Mol Psychiatry, 1999, 4, 317–327.

21. Marques AH, Silverman MN, Sternberg EM: Glucocorticoid dysregulations and their clinical correlates. From receptors to therapeutics. Ann NY Acad Sci, 2009, 1179, 1–18.

22. Marquez C, Nadal R, Armario A: The hypothalamic-pituitary-adrenal and glucose responses to daily repeated immobilization stress in rats: individual differences. Neuroscience, 2004, 123, 601–612.

23. Mizoguchi K, Ishige A, Aburada M, Tabira T: Chronic stress attenuates glucocorticoid negative feedback involvement of the prefrontal cortex and hippocampus. Neuroscience, 2003, 119, 887–897.

24. Mohn CE, Fernandez-Solari J, De Laurentiis A, Bornstein SR, Ehrhart-Bornstein M, Rettori V: Adrenal gland responses to lipopolysaccharide after stress and ethanol administration in male rats. Stress, 2011, 14, 216–226.

25. Müller N, Myint AM, Schwarz MJ: Inflammatory biomarkers and depression. Neurotox Res, 2011, 19, 308–318

26. Munhoz CD, García-Bueno B, Madrigal JL, Lepsch LB, Scavone C, Leza JC: Stress-induced neuroinflammation: mechanisms and new pharmacological targets. Braz J Med Biol Res, 2008 ,41, 1037–1046.

27. Nelson RJ, Trainor BC, Chiavegatto S, Demas GE: Pleiotropic contributions of nitric oxide to aggressive behavior. Neurosci Biobehav Rev, 2006, 30, 346–355.

28. Pariante CM, Lightman SL: The HPA axis in major depression: classical theoriesand new developments. Trends Neurosci, 2008, 31, 464–468.

29. Rettori V, Fernandez-Solari J, Mohn C, Zorrilla Zubilete MA, de la Cal C, Prestifilippo JP, De Laurentiis A: Nitric oxide at the crossroad of immunoneuroendocrine interactions. Ann NY Acad Sci, 2009, 1153, 35–47.

30. Senba E, Ueyama T: Stress-induced expression of immediate early genes in the brain and peripheral organs of the rats. Neurosci Res, 1997, 29, 183–207.

31. Silverman MN, Pearce BD, Biron CA, Miller AH: Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. Viral Immunol, 2005, 18, 41–78.

32. Silverman MN, Sternberg EM: Glucocorticoid regulation of inflammation and its functional correlates: from HPA axis to glucocorticoid receptor dysfunction. Ann NY Acad Sci, 2012, 1261, 55–63.

33. Yamaguchi N, Okada S, Usui D, Yokotani K: Nitric oxide synthase isozymes in spinally projecting PVN neurons are involved in CRF-induced sympathetic activation. Auton Neurosci, 2009, 148, 83–89.

34. Zhou L, Zhu DY: Neuronal nitric oxide synthase: structure, subcellular localization, regulation and clinical implications. Nitric Oxide, 2009, 20, 223–230.