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REVIEW

Blood Pressure Regulation in Stress: Focus on Nitric Oxide-Dependent Mechanisms

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Summary

Stress is considered a risk factor associated with the development of various civilization diseases including cardiovascular diseases, malignant tumors and mental disorders. Research investigating mechanisms involved in stress-induced hypertension have attracted much attention of physicians and researchers, however, there are still ambiguous results concerning a causal relationship between stress and long-term elevation of blood pressure (BP). Several studies have observed that mechanisms involved in the development of stress-induced hypertension include increased activity of sympathetic nervous system (SNS), glucocorticoid (GC) overload and altered endothelial function including decreased nitric oxide (NO) bioavailability. Nitric oxide is well known neurotransmitter, neuromodulator and vasodilator involved in regulation of neuroendocrine mechanisms and cardiovascular responses to stressors. Thus NO plays a crucial role in the regulation of the stress systems and thereby in the BP regulation in stress. Elevated NO synthesis, especially in the initial phase of stress, may be considered a stress-limiting mechanism, facilitating the recovery from stress to the resting levels *via* attenuation of both GC release and SNS activity as well as by increased NO-dependent vasorelaxation. On the other hand, reduced levels of NO were observed in the later phases of stress and in subjects with genetic predisposition to hypertension, irrespectively, in which reduced NO bioavailability may account for disruption of NO-mediated BP regulatory mechanisms and accentuated SNS and GC effects. This review summarizes current knowledge on the role of stress in development of hypertension with a special focus on the interactions among NO and other biological systems affecting blood pressure and vascular function.

Key words

Chronic stress • Endothelial dysfunction • Glucocorticoids • HPA axis • Hypertension

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Introduction

Stress is considered a risk factor associated with the development of various chronic diseases including cardiovascular diseases (CVDs), mental disorders, malignant tumors, diabetes mellitus, obesity, metabolic syndrome, inflammatory and autoimmune disorders and others. Although many different types of stressors exist, psychosocial stressors are apparently the most powerful and exert profound effects on the cardiovascular system (CVS) in humans (Esch *et al.* 2002a). At present stress represents one of the substantial risk factors that modern civilization brings to any society, therefore it has become a public health issue (Franco *et al.* 2003).

Research investigating mechanisms involved in stress-related diseases and pathophysiological changes have attracted much attention of physicians and researchers. However, despite their effort there are still ambiguous results concerning a causal relationship between stress and hypertension.

Although there are numerous definitions of stress, in medicine stress refers to a set of bodily reactions to external and internal factors, e.g. physical,

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psychological, metabolic, infectious and other, which are capable of disturbing homeostasis (Franco *et al.* 2003). In short, biological stress is an organism's response to a stress-provoking stimulus – stressor. Despite the well-known theory of the general adaptation syndrome and Selye´s doctrine of non-specificity (Selye 1936, Selye 1950), marked heterogeneity of neuroendocrine responses to various stressors was shown, suggesting the existence of stressor-specific neurochemical response patterns, depending on the nature (physical, biological, psychosocial), intensity and duration of stressor (Jezova *et al.* 1995, Kvetnanský *et al.* 1998, Pacak *et al.* 1998, Pacák and Palkovits 2001). Thus various stressors may trigger very different biological responses leading to variety of physiological, psychological and behavioral changes and stress-related somatic symptoms. Mravec *et al.* (2009) hypothesized that genetic basis might predispose some individuals to the development of stress-induced diseases due to altered interactions among nervous, endocrine, and immune systems. In human beings, personality, knowledge and previous skills are the other factors affecting the perception of stressor and its health impact (Keller *et al.* 2012). Therefore it is difficult to compare data from various animal stress models or selected human populations. Clinical research on stress-related health consequences is difficult, because there are problems associated with the use of the term "stress", since we have no academic consensus on the definition of stress and subsequently no "standardized stress test" (Ohlin *et al.* 2004, Hovsepian *et al.* 2015). Animal models provide an opportunity to test the role of various stressors in cardiovascular and other diseases and to reveal the mechanisms by which the effects of such stressors are mediated.

Activation of the sympathetic division of autonomic nervous system and hypothalamic-pituitary-adrenocortical (HPA) axis (i.e. corticotropin releasing hormone – CRH, adrenocorticotropic hormone – ACTH and glucocorticoids) are main characteristics of the stress response (Esch *et al.* 2002a, Golbidi *et al.* 2015). These systems promote adaptation to challenges, a process called "allostasis", meaning the process of maintaining stability (homeostasis) despite the change. Nevertheless, these allostatic/adaptive systems also cause problems for the body if their function is inadequate or excessive (McEwen 1998, McEwen 2007). Thus, the organism aims to achieve new stability (allostasis) in new conditions by changes in physiological and behavioral responses (McEwen 2007). However, when stressors are too frequent, long-lasting and/or too intensive, the resulting allostatic load can lead to various diseased states, including hypertension (Fig. 1). On the other hand, the intensity of the stress reaction is determined by the relationship between the activation of the stress systems (mainly sympathetic nervous system, HPA axis) and "stress-limiting systems", which may restrict the excessive activation of the stress systems and, thereby, the detrimental effect of stress. Malyshev and Manukhina (1998) suggested that the system of nitric oxide (NO) generation is such a stress-limiting system, based on the capability of NO to limit key links of the stress reaction.

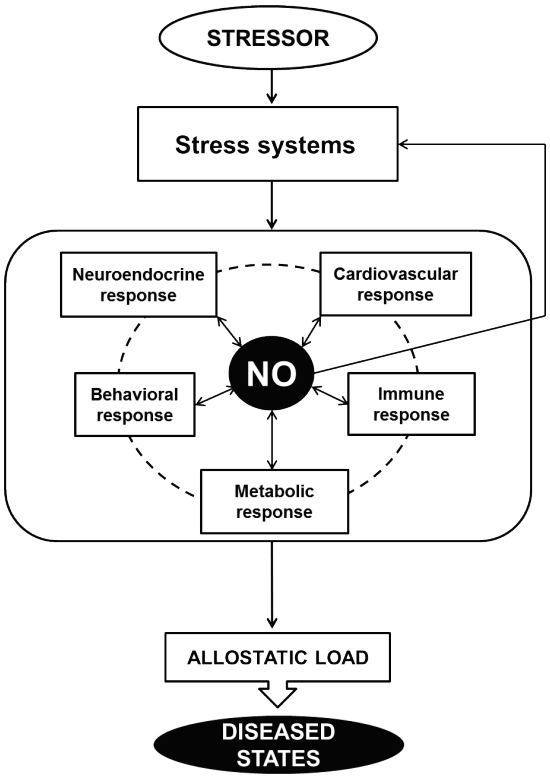

Fig. 1. After exposure to stressor, activation of stress systems leads to cascade of neuroendocrine, cardiovascular, behavioral, metabolic and immune responses, which all were shown to interact with nitric oxide (NO). NO is able to attenuate stress systems. Yet, if stressors are frequent, long-lasting and/or intensive, or if allostatic systems are overactive or underactive or fail to stop after the end of stressful event, the resultant allostatic load can lead to various diseased states.

Nitric oxide is a widespread biological mediator produced in various tissues by one of four isoforms of nitric oxide synthase (NOS: eNOS – endothelial, nNOS – neuronal, iNOS – inducible, mtNOS – mitochondrial) (Guix *et al.* 2005) with the complex regulatory role in the organism. Nitric oxide is well-known neurotransmitter and neuromodulator, significant NO production was

determined in various parts of the central and peripheral nervous system (Steinert *et al.* 2010), vasculature and heart (Pechanova *et al.* 2015) as well as other tissues and organs (Villanueva and Giulivi 2010). NO was shown to be implicated in modulation of responses to stressors suggesting its regulatory role in stress (Malyshev and Manukhina 1998, Bondarenko *et al.* 2001, Esch *et al.* 2002b, Gulati *et al.* 2006, Stefano *et al.* 2006, Gulati *et al.* 2015). Moreover, significant progress was achieved in the characterization of the role of NO as an endothelium-derived relaxing factor in various pathological states, including hypertension. Reduced NO bioavailability is implicated in various experimental models of hypertension as well as in human primary and secondary hypertension (Panza *et al.* 1993, Taddei *et al.* 1998, Ghiadoni *et al.* 2012, Bernatova 2014, Pechanova *et al.* 2015). Yet the exact pathways implicated in the interaction of NO with the mechanisms involved in stress reaction and its contribution to the development of stress-induced hypertension and other CVDs are still matter of experimental research.

At the present time, it is well recognized that stress and NO play an important role in the pathogenesis of CVDs. Acute coronary syndromes (including unstable angina pectoris, myocardial infarction and sudden cardiac death), arrhythmias, stroke (ischemic, hemorrhagic) or transient ischemic attack and stress (Takotsubo) cardiomyopathy are cardiovascular events that may be triggered by acute physical and psychosocial stressors and their impact may be more significant in individuals at high cardiovascular risk (Willich *et al.* 1994, Kirkup and Merrick 2003, Kloner 2004, Wittstein *et al.* 2005, Wilbert-Lampen *et al.* 2008, Steptoe and Brydon 2009, Nalivaiko 2011, Mostofsky *et al.* 2012, Schwartz *et al.* 2012, Struzkova *et al.* 2014, Y-Hassan *et al.* 2015, Barbaryan *et al.* 2016). In addition, chronic stress is considered a significant risk factor of CVDs (Rozanski *et al.* 1999, André-Petersson *et al.* 2001, Esch *et al.* 2002a, Franco *et al.* 2003, Ohlin *et al.* 2004, Steptoe and Kivimäki 2013). There is also a growing body of evidence that psychosocial stressors have an important role in the genesis, onset, progression and manifestation of CVDs (Kaplan *et al.* 1982, Kaplan *et al.* 1983, Manuck *et al.* 1986, Strawn *et al.* 1991, Diez-Roux *et al.* 1995, Helminen *et al.* 1995, Cagan *et al.* 1999, Rozanski *et al.* 1999, Franco *et al.* 2003, Ohlin *et al.* 2004, Toda and Nakanishi-Toda 2011, Golbidi *et al.* 2015). The Interheart case-control study from 52 countries showed that the presence of psychosocial stressors (stress at work and home, financial stress and major life events in the past year) is associated with increased risk of acute myocardial infarction, which was consistent across regions, in different ethnic groups, and in men and women (Rosengren *et al.* 2004).

There is also evidence that acute and chronic stress can induce endothelial injury and dysfunction. The endothelium regulates vascular tone, circulation of blood cells, inflammation and hemostasis. Endothelial dysfunction is considered an early sign of atherosclerosis and early predictor of future cardiovascular events (Daiber *et al.* 2016). CVDs are usually multifactorial and characterized by the presence of one or more risk factors, such as tobacco use, harmful use of alcohol, unhealthy diet and obesity, physical inactivity or sedentary lifestyle, hypertension, diabetes mellitus and dyslipidemia (WHO 2015). Interestingly, all of above mentioned risk factors of CVDs can be associated with stress and endothelial dysfunction (Rozanski *et al.* 1999, Favero *et al.* 2014, WHF 2015, Golbidi *et al.* 2015). Endothelial dysfunction can thus mediate the adverse influence of stressors on cardiovascular health.

Despite many experimental and population-based observational studies, there is still conflicting information about the causal relation between stress and hypertension as studies investigating the effects of chronic stress on blood pressure (BP) produced ambiguous results (Esler *et al.* 2008, Sparrenberger *et al.* 2008). Despite the available data suggesting that chronic stress contributes to the development of hypertension (Timio *et al.* 2001, Pickering 2004, Spruill 2010), the results of experimental studies focused on the mechanisms involved in stress-induced hypertension are inconsistent, yielding both positive and negative evidence on the participation of stress in the development of hypertension (Bobrovskaya *et al.* 2013, Crestani 2016).

This review, though not exhausting, summarizes current knowledge on the role of stress in development of hypertension with a special focus on the interactions among NO and other BP-regulatory systems involved in stress reaction.

Nitric oxide and blood pressure: involvement of eNOS, nNOS and iNOS

Nitric oxide is well known as the most potent vasodilating substance (endothelium-derived relaxing factor), which (besides its other functions) participates in modulation of vascular resistance and heart function and

thus in BP regulation (Török and Gerova 1996, Kunes *et al.* 2004). NO is also involved in stress physiology and stress-related disease processes (Esch *et al.* 2002b, Gulati *et al.* 2006).

The role of NO in CVS was investigated mainly in the model of NO-deficient hypertension, in which NO production was inhibited by N^G-nitro-L-arginine methyl ester (L-NAME), which non-specifically inhibits all NOS isoforms (Víteček *et al.* 2012). Using this model we have shown that chronic pharmacological attenuation of NO synthesis resulted in metabolic alterations and hypertension (Bernatova *et al.* 1996), reduced vasorelaxation and elevated vasoconstriction (Holécyová *et al.* 1996, Bernatova *et al.* 2002b, Pechanova *et al.* 2004a) and arterial wall thickening and myocardial fibrosis (Babal *et al.* 1997) in normotensive rats. Moreover, hypertension induced by chronic NOS inhibition in rats seems to be sustained due to interaction of several mechanisms, including the activation of the sympathetic nervous system (including sympatho-adrenomedullary part) and the renin-angiotensin system (Sander *et al.* 1995, Zanchi *et al.* 1995, Kvetnansky *et al.* 1997, Gerová *et al.* 2004, Pechanova *et al.* 2004b, Zicha *et al.* 2006, Vargas *et al.* 2007, Zicha *et al.* 2009, Behuliak *et al.* 2011, Paulis *et al.* 2012). Rats subjected to chronic administration of L-NAME are thus a useful experimental tool to study the induction and progression of NO deficiency-mediated endothelial dysfunction and hypertension.

On the other hand, mild increase of NO production in the CVS may represent protective mechanism against hypertension, cardiac and vascular remodeling and thus may be involved in cardiovascular protection. Various antioxidants and natural polyphenols, including these isolated from red wine and cocoa were shown to activate NO production and to reduce BP (Bernatova *et al.* 2002b, Pechanova *et al.* 2004a, Galleano *et al.* 2013). Interestingly, we have shown that chronic administration of a low dose of L-NAME can increase NO production in the aorta and left heart ventricle and improve endothelium-dependent vasorelaxation in rats (Bernatova *et al.* 2010) supposedly *via* the negative feedback regulation of NOS (Kopincova *et al.* 2012).

In contrast to chronic L-NAME treatment, chronic administration of structurally different NOS inhibitor, 7-nitroindazole (7-NI), failed to affect BP in normotensive Wistar and spontaneously hypertensive rats (SHR) (Cacanyiova *et al.* 2012, Cacanyiova *et al.* 2014, Kristek *et al.* 2015). Moreover, chronic L-NAME administration inhibited endothelium-dependent relaxation of the thoracic aorta, whereas it remained unchanged after chronic 7-NI treatment in Wistar and SHR rats (Cacanyiova *et al.* 2012, Cacanyiova *et al.* 2014). In addition, neurogenic contractions (induced by transmural nerve stimulation of nerve endings and mediated by endogenous noradrenaline) in mesenteric artery remained unchanged after 7-NI-treatment, but increased after L-NAME-treatment (Cacanyiova *et al.* 2012, Cacanyiova *et al.* 2014). As 7-NI is believed to inhibit predominantly nNOS (Gulati *et al.* 2006, Cacanyiova *et al.* 2014), the roles of eNOS-derived NO and nNOS-derived NO in BP regulation seem to be different. However, it has to be noted that despite enormous effort of researchers to find the substances which would be absolutely specific for either nNOS or eNOS, which would allow us to distinguish NO produced by nNOS from NO produced by eNOS under chronic *in vivo* conditions, are still not available (Alderton *et al.* 2001, Víteček *et al.* 2012). Thus, in contrast to the relatively well-known role of eNOS in BP control, the role of NO produced by the nNOS remains unclear.

Regarding iNOS, excessive amounts of NO produced by this isoform can promote nitrosative stress and endothelial dysfunction. Indeed, Leo *et al.* (2015) showed that L-NAME-mediated inhibition of eNOS was only partially responsible for the vascular pathology observed in this model. Secondary effects of L-NAME treatment may include an increase in iNOS-produced NO and peroxynitrite formation, which may be an important factor for the progression of vascular dysfunction in L-NAME-induced hypertension (Pechanova *et al.* 2004b, Leo *et al.* 2015). Nevertheless, different roles of individual NOS isoforms in BP regulation are supported by the findings in NOS knock-out mice. Functional and morphological alterations observed in L-NAME-induced hypertension (Babal *et al.* 1997) were similar to those observed in mice, in which three NOS isoforms were disrupted, i.e. n/i/eNOS$^{-/-}$ (Tsutsui *et al.* 2010). Moreover, studies that used triple NOS disrupted (n/i/eNOS$^{-/-}$) mice showed that the magnitude of hypertension in the triply NOS$^{-/-}$ disrupted mice were similar to that in mice with the eNOS gene disrupted singly (eNOS$^{-/-}$) or doubly (n/eNOS$^{-/-}$ or i/eNOS$^{-/-}$) (Morishita *et al.* 2005). Furthermore, nNOS knock-out mice did not develop hypertension (Sällström *et al.* 2008). Finally, BP of iNOS$^{-/-}$ mice did not differ from wild type mice in late adulthood (Ihrig *et al.* 2001). Taken together, these studies suggest that hypertension is a common characteristic of the lack of eNOS-produced NO.

Effect of stress on blood pressure

Researchers investigating the regulation of BP during stress have been primarily focused on acute stress. As far as the acute cardiovascular responses to stressors are concerned, the changes of heart rate (HR), BP, cardiac output as well as skin and skeletal muscle blood flow can occur (Lacy *et al.* 1995, Muller *et al.* 2001, Kellerová 2013, Garafova *et al.* 2014). Cardiac output and systemic vascular resistance are the major effector components of neural BP regulation (Grassi and Ram 2016). It is known that acute stress is capable to increase immediately the arterial BP, which is mediated either by an increase in cardiac output or an increase in systemic vascular resistance (Rozanski *et al.* 1988, Lacy *et al.* 1995, Esch *et al.* 2002a, Kellerová 2013). It was shown that men at the high risk for development of hypertension had significantly higher BP accompanied by higher vascular resistance during mental stress compared to low risk subjects. The high and low risk groups had negligible differences in HR, stroke volume, and cardiac output after the exposure to mental stress. This pattern of results implicates vascular resistance as the dominant element in altered BP control in young men at high risk for hypertension (Marrero *et al.* 1997). Importantly, it has been shown that the cardiovascular component of the stress reaction does not require extreme stressors as the increase of BP was evident in daily life already with trivial stimuli, such as watching television (Kellerová 2013, Regecová and Kellerová 2015).

While the role of the brain and the elevated activity of sympathetic nervous system (SNS) in the etiopathogenesis of essential hypertension is widely accepted, the role of stress in the genesis and progression of hypertension and the exact biological mechanisms involved are ambiguous. Prolonged, frequent or repeated exposure to stressors can lead to autonomic nervous system dysregulation and to the changes in the HPA axis and augmented hormone release from the adrenal glands (Golbidi *et al.* 2015). All these changes can lead to cardiovascular dysregulation (see also Fig. 2). Interestingly, the findings of Bobrovskaya *et al.* (2013) suggest that stressors not only alter the BP regulation during the exposure but these alterations persist well beyond the duration of stressor action. Furthermore, the study of Muller *et al.* (2001) suggests a sustained effect of chronic stress on arterial BP regulation after the end of stress.

Several epidemiological studies have demonstrated that individuals chronically exposed to stressful life events and psychosocial stress frequently exhibit persistent hypertension (Timio *et al.* 2001, Pickering 2004). Esler *et al.* (2008) concluded that chronic mental stress is a cause of essential hypertension in humans. On the other hand, Sparrenberger *et al.* (2008) found that recent stressful life events and current psychological distress were not associated with hypertension.

According to Kellerová (2013), psychosocial factors play a permissive role in high BP development. Road traffic noise is a frequent, unavoidable, persistent and continuously increasing environmental stressor to which people are exposed already in the early childhood. Preschool children, attending kindergartens situated in areas with high urban traffic noise, had higher mean systolic and diastolic BP than children in quiet areas (Regecová and Kellerová 1995). In the given study, medium- and high-level urban traffic noise was associated with higher incidence of BP values above the respective 95th percentiles in preschool children. It was also shown that chronic stressful events in early life increase the risk of elevated BP in late adulthood (Alastalo *et al.* 2013). Interestingly, Kellerová (1993, 2013) found that there is a greater increase of systolic and diastolic BP and of HR during bottle feeding than during breast feeding in human neonates, suggesting the protective role of positive emotions. Thus feeding profile may also play a role in early programming of cardiovascular changes.

Several animal studies, which have examined the impact of chronic stress on BP, yielded contradictory results. In normotensive rats, a chronic multiple stress paradigm produced by series of mild, unpredictable stressors elevated resting HR, decreased HR variability, and exaggerated pressor and HR responses to acute air jet stress, but did not lead to sustained increase of mean arterial pressure (MAP) in male Sprague-Dawley (SD) rats (Grippo *et al.* 2002). In normotensive mice exposed to 7-day intermittent shaker stress, significant elevations of MAP and HR were recorded during each shaking session with important circadian changes in pressor responsiveness, but there was no sustained increase of MAP (Bernatova *et al.* 2002a). Another study in mice showed that psychosocial stress produced by crowding induced sustained hypertension (Henry and Stephens-Larson 1984). In contrast, Harrap *et al.* (1984) observed no development of hypertension in normotensive Wistar-Kyoto (WKY) and SD rats subjected to crowding and

isolation stress, respectively. A social stress paradigm, in which normotensive male Wistar and Long-Evans rats were housed with different females, produced no change in basal BP or its circadian rhythm (Lemaire and Mormede 1995). Yet chronic stress produced by social instability due to mixing males from different colonies resulted in hypertension in Long-Evans but not in WKY and SD rats (Henry *et al.* 1993). On the other hand, chronic exposure to various stressors caused elevation of MAP in SD rats (Muller *et al.* 2001). Chronic continuous light exposure (24 h/day), which can be considered a potent stressor, leads to increase in systolic BP in Wistar rats (Simko *et al.* 2010, Repová-Bednárová *et al.* 2013, Simko *et al.* 2014). In addition, in Wistar rats exposed to continuous light, the light-induced increase in sympathetic outflow can suppress BP circadian rhythm (Briaud *et al.* 2004). Other stressor, chronic cold exposure, can induce hypertension in SD, but not in Long-Evans rats (Riesselmann *et al.* 1992). Chronic noise stress caused significant increase in HR and MAP in adult male Wistar rats (Said and El-Gohary 2016). Six weeks of inescapable unpredictable electrical footshocks in adult male Wistar rats significantly reduced body weight gain, locomotor activity and social interaction time (symptoms commonly induced by chronic stress and depression in humans) and were associated with elevation of systolic BP and pulse pressure and modifications in sympathoadrenal pathways (Bobrovskaya *et al.* 2013). Sustained MAP elevation was reported after chronic stress in male SD rats that responded to acute stressor *via* elevated systemic vascular resistance, i.e. in vascular responders, but not in responders responding by an increase in cardiac output (Muller *et al.* 2001). The development of hypertension and cardiac pathology such as cardiac fibrosis or coronary vascular wall hypertrophy were observed in young 4-week-old normotensive rats exposed to chronic isolation followed by territorial stress or exposed to territorial stress alone (Andrews *et al.* 2003).

Several studies demonstrated the importance of genetic background in stress-induced pressor responses in rats with various family history of hypertension (Fisher and Tucker 1991, Hatton *et al.* 1993, Tucker and Hunt 1993, Li *et al.* 1997, Mansi and Drolet 1997, McDougall *et al.* 2000) suggesting that positive family history of hypertension may be an important factor in the development of stress-induced hypertension. Thus, normotensive animal models, without family history of hypertension, need not be always appropriate tools for investigation of stress/hypertension association. For such studies, a more suitable model – borderline hypertensive rats (BHR) – with a family history of hypertension is produced by the mating of spontaneously hypertensive dams (or sires) with normotensive sires (or dams) (Lawler *et al.* 1980, Sanders and Lawler 1992, Šarenac *et al.* 2011, Zemančíková and Török 2015). The advantage of this model is that BHR are more sensitive to behavioral stress than normotensive rats and they do not develop severe age-related hypertension as do SHR rats. BHR exhibit various cardiovascular abnormalities like myocardial hypertrophy, sympathetic hyperresponsiveness (demonstrated by tachycardia and high sensitivity of arterial contractile responses to noradrenergic stimulation) and endothelial dysfunction in various arteries (Puzserova *et al.* 2013a, Zemančíková and Török 2015). These findings support the idea that in BHR the increased BP level (as compared to WKY rats) is associated with a higher sympathetic activity. The use of chronic psychosocial models of stress in BHR resulted in the development of hypertension, heart hypertrophy and significant cardiac pathology (Lawler *et al.* 1981, Sanders *et al.* 1989). Our studies also point to genotype-related differences in stress-induced pressor responses in young female and male rats as well as in adult male rats (Bernatova *et al.* 2007a, Slezak *et al.* 2014, Bernatova *et al.* 2015). In our studies, chronic crowding stress applied in young BHR and SHR females during sensitive BP developmental window (i.e. at the age of 5-7 weeks) (Zicha and Kunes 1999) led to the acceleration of BP increase in BHR, but not in age-matched WKY and SHR, in which genetic predisposition to hypertension was a predominant factor in development of BP in young age (Slezak *et al.* 2014). Thus young BHR rats were more vulnerable to stress than the offspring of two normotensive or two hypertensive parents. These studies showed that the exposure of genetically predisposed subjects to stress, especially in a sensitive developmental period of life, can trigger the onset of hypertension development to earlier periods of life.

In adult male rats, chronic crowding resulted in a significant increase of BP in SHR-mothered BHR and SHR compared to controls but not in Wistar, WKY and Wistar-mothered BHR (Puzserova *et al.* 2006, Bernatova *et al.* 2007a). However, in some studies even a chronic stress exposure of BHR (aggregation or social instability) failed to result in stress-induced hypertension, although typical signs of stress such as reduced weight gain, adrenal hypertrophy, elevation of plasma noradrenaline

(NA) and increase of left and right heart ventricle mass were observed (Harrap *et al.* 1984, Gelsema *et al.* 1994, Lemaire and Mormede 1995). Similarly, ten days of air-jet stress (2 h/day) failed to increase the baseline values of MAP and HR in male BHR and WKY rats aged 14-16 weeks (Fuchs *et al.* 1998). However, these authors found that changes in vascular reactivity induced by stress appear to correlate with, and may contribute to, the different hemodynamic adaptations to repeated stressors observed in WKY and BHR rats.

Finally, various factors that potentially contribute to controversial results of above mentioned animal studies may include different type of stressors, the duration of their action, the animal´s age, sex and strain as well as the method used to assess arterial BP (Nalivaiko 2011).

Endothelial function in stress

Nervous, humoral and endothelial vasomotor controls are important factors in systemic cardiovascular homeostasis and BP regulation (Gerová 2000, Kellerová 2013, Bernatova 2014). As mentioned above, endothelium regulates vascular tone, i.e. influences the contractile activity of vascular smooth muscle by releasing contracting factors (EDCFs – endothelium-derived contracting factors) such as endothelin-1 or angiotensin II and relaxing factors (EDRFs – endothelium-derived relaxing factors) such as NO, prostacyclin (PGI_2), hydrogen sulfide (H_2S) and endothelium-derived hyperpolarizing factor(s) (EDHFs). In addition, the endothelium regulates the proliferation/ growth of the underlying smooth muscle, and also acts as a barrier to control the exchange of nutrients, biomolecules and messengers between the blood and surrounding tissues. The EDRFs also possess antiaggregatory properties and suppress thrombus formation (Daiber *et al.* 2016). Endothelial dysfunction, which includes an impairment of endothelium-dependent vasorelaxation (Bernatova 2014), is associated with various CVDs, including hypertension. Although the involvement of alterations in endothelium-derived NO in stress-related hypertension is not clearly defined, there are both animal and human studies showing the involvement of peripheral vascular changes in this particular type of hypertension.

Acute exposure to stressors influences vasomotion in different vascular beds. In humans, blood flow redistribution occurs from the visceral and cutaneous beds toward the skeletal and heart muscle vasculature during acute stress, which is mediated mainly by vasoconstriction in the splanchnic, renal and cutaneous vascular beds and by vasodilatation of the muscle vasculature (Kellerová 2013, Crestani 2016).

In healthy volunteers elevated forearm blood flow, specifically endothelial NO-mediated, was observed after acute mental stress (Dietz *et al.* 1994). Similarly, Carter *et al.* (2005) found mental stress induced forearm vasodilatation, which was not associated with changes in muscle sympathetic outflow. The involvement of local NO release in the forearm vasodilator response to acute mental stress in humans was detected by Cardillo *et al.* (1997). Interestingly, acute psychological and physical stress transiently enhances brachial artery flow-mediated dilation stimulated by exercise in healthy men (Szijgyarto *et al.* 2014).

In contrast, there are studies showing that brief episodes of mental stress induced endothelial dysfunction in both brachial and radial arteries of healthy subjects without cardiovascular risk factors (Ghiadoni *et al.* 2000, Spieker *et al.* 2002). Spieker *et al.* (2002) showed that mental stress lasting 3 min induced a prolonged endothelial dysfunction, which was prevented by selective endothelin-A receptor antagonism in healthy subjects without cardiovascular risk factors. Similarly, mental stress induced reduction of brachial artery flow-mediated endothelium-dependent dilation in subjects with metabolic syndrome (Sales *et al.* 2014). In patients with essential hypertension and with chronic myocardial infarction an abnormal vasomotor reactivity was induced by acute emotional stress, suggesting the presence of endothelial dysfunction (Kellerová 2013). In addition, acute mental stress can trigger transient myocardial ischemia, often silent, in patients with coronary artery disease (Rozanski *et al.* 1988). Furthermore, increased sympathetic tone induced by mental stress can cause acute coronary vasoconstriction (instead of vasodilatation) also in patients without angiographically demonstrable coronary artery disease (Lacy *et al.* 1995). Together, these studies suggest that short episodes of stressor exposure, similar to those encountered in everyday life, may cause transient endothelial dysfunction also in healthy young individuals and the presence of endothelial dysfunction and atherosclerotic plaques may result in abnormal vascular reactivity to stressors. However, the exact mechanisms which impair endothelial function in stress are still not clearly defined.

Animal studies revealed several mechanisms that

are involved in the disruption of endothelial function in stress. Short-term social stress caused an increase in HR and a damage of the endothelium in the thoracic aorta and coronary artery in monkeys, which was prevented by the treatment with ß-adrenergic blocking agent metoprolol (Strawn *et al.* 1991). Williams *et al.* (1993) suggested that repeated episodes of acute sympathetic stimulation result in sharp increases of BP and HR, which may damage the vascular endothelium and impair the release or augment the breakdown of NO. Signs of endothelial injury, rise in endothelemia and von Willebrand factor concentrations, were also observed early after acute immobilization stress in adult male (Jezova *et al.* 2003) and female SD rats (Kristova *et al.* 2006). Thus vascular damage, including changes in endothelial function, can occur before the development of hypertension (Fuchs *et al.* 1998) and may accelerate its onset.

Regarding chronic stress, little information is available on its impact on endothelial function in humans because of methodological and ethical limitations. More information on the mechanisms involved in altered vascular function during chronic stress is available from experimental studies in monkeys and rodents.

Chronic psychosocial stress in monkeys impaired endothelium-mediated dilatation of coronary arteries (Williams *et al.* 1991). In addition, chronic psychosocial stress reduced receptor-mediated release of NO by acetylcholine (ACh), non-receptor-mediated release of NO by the calcium ionophore A23187, without changes in endothelium-independent NO-mediated vasorelaxation to nitroprusside in the iliac arteries isolated from monkeys fed with atherogenic diet (Williams *et al.* 1993). Reduced endothelium-dependent relaxation to ACh was observed in the aorta of socially isolated female prairie voles (Peuler *et al.* 2012). Similar finding was observed in the thoracic aortas of male mice subjected to unpredictable chronic mild stress (Insingrini *et al.* 2011). Neves *et al.* (2009) also found that chronic unpredictable stress induces functional changes in the aorta of male SD rats which may be related to decreased NO bioavailability. These studies suggest that chronic stress may downregulate NO production and/or bioavailability. The impairment of NO production in long-term stress may result from sudden and repeated pressure fluctuation (Fokkema *et al.* 1986) that could damage the endothelial monolayer and alter the vascular wall structure. In Wistar-mothered BHR, electron microscopy showed that chronic crowding-induced injury of endothelial cells in the aorta is characterized by mitochondrial damage, presence of vacuoles, increased number of lysosomes, Weibel-Palade bodies, changes of intercellular connections and local disruption of endothelium, while only slight changes were seen in Wistar rats (Okruhlicova *et al.* 2008). This might also result from the fact that connexin 43 expression was reduced in the aortic endothelium already in prehypertensive period, which may affect cell-to-cell communication and thus participate in acceleration of hypertensive disease in stress in genetically predisposed rats (Dlugosova *et al.* 2008). These results suggest increased vulnerability of endothelium of rats with genetic predisposition to hypertension to stress-induced damage that may contribute to acceleration of arterial dysfunction and hypertension development following stress.

Regarding the functional endothelial changes, most of the studies investigated total endothelium-dependent vasorelaxation and did not take into account individual components of vasodilatation mediated by different EDRFs. Thus, it remains unclear, if chronic stress might impair endothelium-mediated dilation only due to reduced bioavailability of NO. Furthermore, it is unknown if the effects of stress on endothelial function can be reversed by removing the stressor. However, Williams *et al.* (1993) found that previous chronic stress lasting 18 months did not have persisting effects on endothelium-dependent NO-mediated dilatation after 18 months of stress. The same authors also found that the deleterious effect of psychosocial stress on endothelium-mediated dilation was not mediated through the products of the cyclooxygenase (COX) pathway. Peuler *et al.* (2012) observed that chronic social isolation caused an enhancement of ACh-induced contraction in non-precontracted endothelium-intact aortae. Such an enhancement of ACh-induced contraction suggests abnormally excessive release of EDCFs from the endothelium. The excessive release of EDCFs, mainly COX-dependent, has been demonstrated repeatedly in arteries of hypertensive rats and humans (Paulis *et al.* 2008, Virdis *et al.* 2010, Líšková *et al.* 2011, Vanhoutte 2011, Puzserova *et al.* 2013a, Puzserova *et al.* 2014). EDCFs can effectively counteract the endothelium-dependent vasorelaxation, including its NO-mediated component (Dai *et al.* 1992). In addition, EDCFs contribute to NA-induced contractions and this effect is enhanced in conduit arteries of SHR (Líšková *et al.* 2011). Moreover, acute NOS inhibition enhanced the contribution of EDCFs to NA-induced contraction

(Líšková *et al.* 2011). The contractile hyperreactivity to angiotensin II in carotid artery of acutely restrained diabetic rat is also mediated by metabolites derived from COX-2, highlighting the harmful role of acute stress in modulation of diabetic vascular complications (Moreira *et al.* 2015). These results show that the impairment of the interplay between NO, EDCFs and NA is an important mechanism which may be involved in stress-linked hypertension.

On the other hand, there are reports of opposite endothelial responses induced by chronic stress. Increased endothelium-dependent vasodilator responses of the aorta were observed in mice made hypertensive by the exposure to chronic social stress in a complex population cage (Webb *et al.* 1987). Similar findings were observed also in male Wistar rats submitted to chronic immobilization stress (Bruder-Nascimento *et al.* 2015). Chies *et al.* (2003) reported that chronic forced swimming stress may increase non-endothelial NO activity in both the aorta and superior mesenteric artery of adult male Wistar rats. In male Wistar rats the vascular adaptive response to chronic and acute stress was characterized by hyperactivity of the endothelial L-arginine/NO system (Cordellini and Vassilieff 1998, Cordellini *et al.* 2006) and this adaptive response was impaired in SHR, independently of the hypertensive state (prehypertensive or hypertensive) (Cordellini *et al.* 2006). These findings indicate that chronic stress can promote adaptive vascular NO-dependent responses.

To elucidate the effect of chronic stress on NO-dependent component of relaxation, we used stress produced by crowding in rats. Crowding is a typical social stressor (Bugajski 1999, Gavrilovic and Dronjak 2006, Myslivecek and Kvetnansky 2006). In humans, crowded residents had higher levels of urinary catecholamines and greater increases in BP and HR during performance of a challenging task than uncrowded residents (Fleming *et al.* 1987), suggesting a deleterious effect of chronic crowding on cardiovascular regulation. Although crowding is a relatively mild stressor, it has a considerable effect on the HPA axis and the sympathoadrenomedullary system (SAS) in rats (Djordjevic *et al.* 2003, Dronjak *et al.* 2004).

In our studies, the effect of chronic social stress on endothelium-dependent vasorelaxation mediated by NO was tested in the femoral and mesenteric arteries. The functional status of the endothelium was tested by the ACh test in isolated preconstricted arteries. However, ACh-induced relaxation results from stimulated release of at least three different vasodilating agents released from the endothelial cells – NO, PGI_2, and EDHFs (Puzserova *et al.* 2013a). Under the normal conditions, NO seems to be the most powerful vasorelaxing factor, however, the extent of NO-dependent relaxation depends on the size of the artery. The biggest NO dependency of endothelium-dependent relaxation was observed in the aorta, while the role of NO is much smaller in the small resistant arteries where EDHFs seem to be more important (Shimokawa *et al.* 1996). We observed increased endothelium-dependent ACh-induced relaxation and its NO-mediated component in the femoral artery of adult male WKY (Puzserova *et al.* 2006, Bernatova *et al.* 2007b, Puzserova and Bernatova 2010) and Wistar rats (Bernatova *et al.* 2007a) exposed to crowding for 8 weeks. Concurrently, a reduction of NO-independent relaxation was found in the femoral artery from male WKY rats after 8-week crowding (Puzserova *et al.* 2013b). However, chronic crowding failed to alter endothelial function of the superior mesenteric artery and its first branches in adult male WKY rats (Puzserova *et al.* 2012). Interestingly, in the presence of the potent antioxidant, ascorbic acid, the elevated endothelium-dependent relaxation was found in the mesenteric arteries from stressed WKY rats (Bernatova *et al.* 2007b), suggesting an important role of reactive oxygen species (ROS). Furthermore, 2-week crowding elevated NO production and superoxide concentration in pubertal female WKY rats, which resulted in reduced NO-dependent relaxation of the femoral artery (Slezak *et al.* 2014).

Despite the fact that 8-week crowding led to elevated NOS activity and nitrate/nitrite (stable NO metabolites – NOx) levels in the aorta of adult WKY male rats, stress failed to affect BP, HR and plasma NOx levels (Puzserova *et al.* 2006, Bernatova *et al.* 2007b, Puzserova and Bernatova 2010, Puzserova *et al.* 2013b). Interestingly, in male Wistar rats we observed only a tendency towards elevation of NOS activity in the aorta using the same stress model (Bernatova *et al.* 2007a, Bernatova *et al.* 2010). In addition, the treatment of Wistar rats with a low dose of L-NAME, which produced only temporal increase of BP, precluded the stress-induced enhancement of endothelium-dependent relaxation of the femoral artery and resulted in a gradual BP elevation (Bernatova *et al.* 2010).

The prolongation of crowding to 12 weeks in WKY rats still failed to increase BP, but resulted in a reduction of overall endothelium-mediated vasorelaxation of the femoral artery. This was still

associated with elevated NOS activity in the aorta and elevated NO-dependent component of ACh-induced relaxation of the femoral artery. However, reduction of the NO-independent component (i.e. mediated by EDHFs and/or PGI_2) of relaxation was observed also in these rats, which was more pronounced after 12-week vs. 8-week crowding (Puzserova *et al.* 2013b). Our findings indicate that extended crowding is associated with endothelial dysfunction and reduced NO-independent relaxation despite increased NO production. Similar findings were observed using 8-week mild stress in rats (Bouzinova *et al.* 2014). The authors found that NO-dependent relaxation and eNOS expression were increased in small mesenteric arteries from stressed anhedonic rats compared with the non-stressed rats. In addition, inhibition of COX activity revealed increased COX-2-dependent relaxation in the anhedonic group. In contrast, eNOS-independent and COX-independent relaxation to ACh, i.e. endothelium-dependent hyperpolarization-like component of relaxation, was reduced in stressed anhedonic rats, which was associated with decreased transcription of intermediate-conductance Ca^{2+}-activated K^+ channels (Bouzinova *et al.* 2014). Another study demonstrated that the overall endothelium-dependent relaxation to ACh was not altered quantitatively, but there were alterations in the mechanisms mediating relaxation in chronically stressed WKY and BHR rats (Fuchs *et al.* 1998). It was found that exposure to 10 days of behavioral stress enhanced the role of vasodilator COX products in small mesenteric arteries of WKY rats (Fuchs *et al.* 1998). However, the inhibition of NOS activity had a significantly larger inhibitory effect on ACh-induced relaxation (suggesting an enhanced role of NO) in small mesenteric arteries from stressed BHR rats (Fuchs *et al.* 1998). In our studies 8-week chronic social stress reduced NOS activity in the aorta of adult male BHR and SHR (Bernatova *et al.* 2007a) in contrast to normotensive rats. In contrast, 2-week crowding stress significantly elevated NO production in the aorta of pubertal female BHR and SHR (Slezak *et al.* 2014) while only a non-significant increase was observed in age-matched males (Bernatova *et al.* 2015). Similarly, in pubertal BHR males there were no differences in endothelium-dependent vasorelaxation of the femoral artery, including its NO-dependent and NO-independent components, between the stressed and control groups (Bernatova *et al.* 2015).

These studies demonstrated that long-term psychosocial stress (both crowding and mild unpredictable stress model) can reduce endothelium-dependent relaxation due to suppressed NO-independent component of relaxation in various arteries, while the NO-dependent component of relaxation may remain elevated. Thus, NO-independent endothelial dysfunction might be the initial step in the development of stress-induced CVDs, including vascular remodeling followed by atherosclerosis and/or hypertension in normotensive subjects. In contrast, according to our studies, vascular L-arginine/NO system supposedly protects adult male normotensive rats from the development of stress-induced hypertension. However, the ability of NOS to produce NO may be variable in the course of stress and this protective system may be subsequently insufficient to balance vasoconstriction and BP elevation in stress. Moreira *et al.* (2016) suggested that behavioral stress-induced increases in NO production may trigger a massive impact on vascular cells and to accelerate cardiovascular complications under oxidative stress conditions as it was described in diabetes mellitus.

Yet, it is noteworthy that the effect of stress on vascular endothelial function may differ at various arterial sites because of different local hemodynamic milieu and arterial receptor number and function.

How can stress influence the endothelium-dependent NO-mediated vascular function?

Despite many discrepancies, several possible mechanisms for endothelial damage following stress have been described. The stressor-induced activation of the SNS and HPA axis, resulting in the secretion of catecholamines and glucocorticoids, can alter endothelial and vascular smooth muscle cell function by triggering the secretion of endothelial endothelin-1, cytokines and the production of ROS (Ullian 1999, Nickel *et al.* 2009, Goodwin and Geller 2012). It was shown that hemodynamic factors, for example elevations in HR and associated blood flow disturbances, can contribute to early endothelial damage in stress (Strawn *et al.* 1991, Skantze *et al.* 1998). Skantze *et al.* (1998) pointed out that psychosocial stress (socially unstable condition for 72 h) induces endothelial injury in adult male cynomolgus monkeys, and this effect was mediated *via* β_1-adrenoceptor activation. In humans, sympathetic stimulation, at a clinically relevant range, significantly impaired endothelium-dependent flow-mediated dilation by an α-adrenergic mechanism (Hijmering *et al.* 2002). Pettersson *et al.* (1990) demonstrated the relation between adrenergic activation, HR and endothelial injury

both in unbranched and in circumostial areas of arteries.

It is well known that blood vessels *in vivo* are constantly under the influence of hemodynamic forces, including shear stress, hydrostatic pressure and cyclic strain. Hemodynamic forces, which are altered during increased sympathetic arousal, are important determinants of vascular homeostasis and may be involved in stress-related vascular reactivity changes. Shear stress, which is the tangential frictional force acting on the vascular endothelial cells due to blood flow, has been shown to mediate blood flow-induced vasodilatation (Smiesko *et al.* 1985, Cábel *et al.* 1994). Graded increase in shear stress promotes eNOS expression and activity, leading to enhanced NO formation (Hsieh *et al.* 2014, Sriram *et al.* 2016). High blood flow-induced shear stress is also an important factor in the NO-dependent regulation of peripheral vascular resistance (Smieško and Johnson 1993). Irregular or disturbed flow pattern and shear stress result in higher levels of ROS which reduce NO bioavailability (Hsieh *et al.* 2014). In this regard, oxidative stress is an important determinant in the development of endothelial dysfunction (Payne *et al.* 2003, Daiber *et al.* 2016). Additionally, ROS alter prostaglandin metabolism, endothelin-1 signaling and H_2S-mediated mechanisms (Bernatova 2014) and promotes novel oxidative posttranslational protein modifications that interfere with endothelial signaling. In addition to the reduction of bioavailable NO, ROS may also reduce endothelium-dependent hyperpolarization and PGI_2 synthesis (Bachschmid *et al.* 2013), promoting the arterial contraction. Moreover, increased concentration of ROS or oxidative stress markers were documented in acute and chronic stress in both human and animal studies (Sivonová *et al.* 2004, Zafir and Banu 2007, Kwiecien *et al.* 2008, Zafir and Banu 2009, Takaki 2013, Moreira *et al.* 2015, Moreira *et al.* 2016, Said and El-Gohary 2016).

In our study, the application of 2-week crowding in young female rats elevated aortic ROS only in WKY rats, while a decrease of aortic ROS was observed in SHR (Slezak *et al.* 2014). This surprising finding may result from a better capacity of the antioxidant defense system in young (pre)hypertensive rats, which may be damaged in later periods of life (Horvathova *et al.* 2016). On the other hand, ROS possess an important role in signal transduction. Very recently we have shown that the lack of ROS resulted in greater stress-induced MAP decrease and prolongation of time required to reach new post-stress steady state of BP in acutely air-jet stressed rats with inhibited SNS function and NO production, showing an important role of ROS in BP regulation during acute stress (Bernatova *et al.* 2016). Furthermore, the involvement of HPA axis in the alterations of endothelial NO activity is described below.

Interactions of NO with SNS in stress

It is well known that sympathetic activation plays a significant role in BP regulation in both normal and pathological conditions. It has also an important role in the development of stress-induced hypertension. In humans, elevated sympathetic nerve activity contributes to the pathogenesis of essential hypertension (Penesova *et al.* 2008, Garafova *et al.* 2014, Grassi and Ram 2016) and the interventions targeting sympathetic activation have been considered as an important strategy for attenuating hypertension (Mancia *et al.* 2013). Moreover, essential hypertensive patients have greater sympathetic reactivity in response to acute stress (Kaushik *et al.* 2004, Kellerová 2013, Garafova *et al.* 2014). Several studies suggested reciprocal inhibitory effects between SNS activity and NO, both in the vasculature and central nervous system (CNS). Hence, the mechanisms involved in the development of stress-induced hypertension may include the dysregulation of SNS and coupled NO pathways (Esch *et al.* 2002a).

Central NO is hypothesized to participate in the regulation of autonomic function by decreasing sympathetic output to the periphery. Deficient neuronal NO production is thought to cause sympathetic overactivity that can contribute to NO-deficient hypertension (Sander and Victor 1999). In Wistar rats, inhibition of NOS in posterior hypothalamic area, which is involved in central cardiovascular regulation, induced BP increase (Gerová *et al.* 1995). Similarly, Shapoval *et al.* (1991) demonstrated an increase in BP after NOS inhibition in the vasomotor centers of the ventrolateral medulla. Sander *et al.* (1995) prevented BP increase after NOS inhibition by pharmacological peripheral sympathectomy. However, more recent experimental studies showed that NO signaling in the brain may be both pro- and anti-hypertensive, depending on the area of the brain and NOS isoform. Inhibitory effect of e/nNOS-produced NO on SNS activity was observed in hypothalamic paraventricular nucleus (PVN) (Zhou *et al.* 2014) and eNOS-produced NO in the nucleus tractus solitarii (NTS) (Cheng *et al.* 2013, Wu *et al.* 2016). Chronic interference of nNOS dimerization required for generation of NO within the PVN potentiated the increase

of BP by modulating the sympathoexcitation that accompanies renovascular hypertension (Rossi *et al.* 2010). NO has also been shown to inhibit renal sympathetic outflow by modulating local GABAergic activity within the PVN (Zhang and Patel 1998). In propofol-anesthetized rats, nNOS-derived NO at the rostral ventrolateral medulla (RVLM) induced sympathoexcitation *via* both N-methyl-D-aspartate (NMDA) and non-NMDA receptors while NO generated by iNOS elicited sympathoinhibition *via* $GABA_A$ receptors (Chan *et al.* 2003). In contrast, chronic overexpression of iNOS in the RVLM of normotensive rats increased BP *via* SNS activation and oxidative stress (Kimura *et al.* 2005). Moreover, iNOS levels in the RVLM were significantly higher in SHR than in WKY rats and microinjection of aminoguanidine (iNOS inhibitor) into the RVLM dose-dependently decreased BP and HR in SHR, but not in WKY rats. These findings suggest that iNOS expression in the RVLM of SHR contributes to BP increase (Kimura *et al.* 2009). On the other hand, overexpression of eNOS in rat RVLM decreased BP, HR and urinary excretion of NA, indicating that eNOS lowers the central sympathetic outflow (Kishi *et al.* 2001).

Accumulating evidence for a modulation of sympathetic neurotransmission by endogenously produced NO shows that NO restricts the release of sympathetic transmitters at the level of adrenal medulla (Torres *et al.* 1994, Zanchi *et al.* 1995, Kvetnansky *et al.* 1997) and at nerve terminals of the heart and vessels (Addicks *et al.* 1994, Schwarz *et al.* 1995, Kyselá and Török 1997). L-NAME-treated rats had markedly increased plasma levels of adrenaline, NA and dopamine metabolites at rest and during immobilization stress (Kvetnansky *et al.* 1997). A significant increase of NOS activity in the adrenal medulla was observed in the acutely immobilized animals (Kishimoto *et al.* 1996). Thus NO may efficiently suppress the stress discharge of catecholamines from the adrenal glands. In addition, NO from adrenomedullary chromaffin cells could be implicated in the autoinhibitory process of catecholamine release (Torres *et al.* 1994). These findings demonstrated that adrenaline, dopamine and NA release at the periphery is under the inhibitory control of endogenous NO. On the contrary, Orlando *et al.* (2008) found that the absence of nNOS-derived NO in nNOS knock-out mice reduced the capacity of adrenaline-synthesizing enzymes in the adrenal glands to respond to acute stressor exposure with an adequate adrenaline release.

In the vasculature, NA is the main neuromediator of SNS. In healthy animals the vasodilating EDRFs are produced in large amounts enabling the endothelium to oppose the vasoconstricting tone generated by the activity of the SNS. NO inhibits NA-dependent vascular contraction and by this mechanism it is capable to lower arterial BP. Thus under normal conditions the endothelial NO negatively modulates the activity of the adrenergic portion of sympathetic neurotransmission (Török 2008). Endothelial damage impairs the balance between vasoconstriction and vasodilatation (Holécyová *et al.* 1993). The studies, in which NO production was reduced by acute non-specific inhibition of NOS showed immediate BP increase, indicating that NO counteracts the vasopressor effects of SNS (Zicha *et al.* 2014). Indeed, L-NAME-induced hypertensive response was significantly attenuated with chronic α- and β-adrenergic receptor blockade in diabetic rats (Fitzgerald and Brands 2002). Similarly, Dobesova *et al.* (2002) confirmed the major importance of both sympathetic hyperactivity and relative NO deficiency for the maintenance of salt hypertension in Dahl rats. Interestingly, using a sequential blockade of renin-angiotensin system (RAS), SNS and NOS Kuneš *et al.* (2004) revealed a characteristic imbalance between sympathetic activity and relative NO deficiency in most of the examined models of experimental hypertension. In addition to these facts, the important role of NO in limiting the peripheral action of catecholamines is supported by the findings that inhibition of NO synthesis results in hypertension, as mentioned above.

Increased BP in SHR is usually caused by high activity of SNS. Yet in SHR, in which elevated SNS activity (Okamoto *et al.* 1967, Lee *et al.* 1991, Korner *et al.* 1993, Paulis *et al.* 2007, Pintérová *et al.* 2010, Zicha *et al.* 2014) and increased NA release from the hypothalamus (Qualy and Westfall 1988, Pacák *et al.* 1993) were observed, contradictory findings were published with regard to NO production in the various brain areas. Reduced nNOS activity and protein expression were found in the brainstem but not in the diencephalon of adult SHR (Hojná *et al.* 2010). In contrast, elevated eNOS expression was observed in the brainstem of SHR in another study of this research group (Hojná *et al.* 2007). No changes in nNOS gene expressions were found in 4-week-old (pre-hypertensive) SHR in the hypothalamus, dorsal pons, dorsal medulla, RVLM and caudal ventrolateral medulla while elevated nNOS were determined in the hypothalamus, dorsal

medulla and caudal ventrolateral medulla of 14-week-old SHR vs. age-matched WKY or SD rats (Plochocka-Zulinska and Krukoff 1997). These data show that gene expression of nNOS is increased in central autonomic centers in animals with increased sympathetic activity and they support the hypothesis that NO plays an important role in the maintenance of homeostatic balance through the attenuation of sympathetic activity (Plochocka-Zulinska and Krukoff 1997). We have observed unchanged NOS activity in the hypothalamus of adult male SHR despite elevated BP and HR (Bernátová 2006, Bernatova *et al.* 2007a). Discrepancies seem to result from differences in the age, methods used for determination of NO production (i.e. individual NOS gene expression, protein expression or NOS activity) and studied areas of the brain. On the other hand, the failure to correct spontaneous hypertension by NO donors administration (Kristek *et al.* 2003) reflects the fact that sympathetic overactivity plays a key role in this form of hypertension, while NO production in SHR might be enhanced to compensate increased BP (Török 2008, Púzserová *et al.* 2013a, Zicha *et al.* 2014).

Regarding stress conditions, it was found that NO production is considerably modified in the SNS and HPA system during stress and is related to the duration of stress (acute vs. chronic) as well as the time-course of chronic stress. Accentuated expression of nNOS mRNA was observed in the PVN of acutely restrained rats (de Oliveira *et al.* 2000) and elevated nitrate/nitrite levels were observed in PVN dialysate of shaker-stress exposed rats (Kawa *et al.* 2002). The elevation of NOS activity and nNOS mRNA expression was observed in the PVN of rats exposed to short-term immobilization (Kishimoto *et al.* 1996). Furthermore, the rise in angiotensin II type 1 (AT_1) receptor mRNA levels in the hypothalamus and hippocampus after stress or repeated treatment with L-NAME as well as the correlation between AT_1 receptor mRNA and NOS mRNA in the brain suggest an interaction between the central angiotensin II and NO (Kiss *et al.* 2001, Krizanova *et al.* 2001). The importance of NO formation in the brain to counteract stimulatory effects of central angiotensin II on the sympathetic tone was also suggested (Dampney *et al.* 2005).

Interesting data were provided by Leza *et al.* (1998) who found the elevation of brain NOS activity and cyclic guanosine monophosphate (cGMP) content in lean rats after 4 and 9 days of stress while normal levels were seen after 14 days. These authors also suggested that the role of NO during chronic stress in the brain appears to be detrimental as this molecule mediates glutamate-dependent hippocampal damage during chronic stress. In contrast, increased generation of NO in the vascular system may attenuate the vasoconstrictor and platelet aggregatory effects of catecholamines and other mediators of stress (Leza *et al.* 1998).

In our studies, 8-week crowding had no effect on hypothalamic NOS activity in adult Wistar, Wistar-mothered BHR, SHR-mothered BHR and SHR rats (Bernatova 2006, Bernatova *et al.* 2007a). It is of interest that in young male rats, both WKY and SHR-mothered BHR, 2-week crowding reduced NOS activity in the brainstem, cerebellum and hypothalamus and these changes persisted two weeks after cessation of crowding, while in a tendency of increased NOS activity was seen in the aorta of stressed rats (Bernátová *et al.* 2015). In line with our studies, total NOS activity in the hypothalamus and nNOS-immunoreactive cell density in the PVN were both significantly decreased while plasma NO and corticosterone (pCort) levels were elevated in the rats exposed to chronic unpredictable stress (Gao *et al.* 2014). This finding suggests that NO production in the circulation and in the brain may be differently affected by chronic stress.

Regarding the periphery, a number of studies have assessed stress-induced changes in adrenergic vasoconstriction, but the findings are variable. Parra *et al.* (1994) evaluated the effect of either 7-14 or 30-35 days of social deprivation stress in Wistar rats on constriction of the aorta. Interestingly, constriction of the aorta to NA was impaired after 7-14 days of stress while 30-35 days of stress resulted in elevation of aortic constriction, suggesting the differences in the course of stress. Acute and chronic stress in normotensive Wistar rats caused a decrease in the reactivity of blood vessels to adrenergic stimuli (Cordellini and Vassilieff 1998, Cordellini *et al.* 2006). In these studies, the enhanced role of NO was suggested, because L-NAME administration and endothelium removal abolished the stress-induced aortic hyporeactivity (Cordellini *et al.* 2006) and the SAS participated in hyperactivity of the endothelial NO system induced by stress (Navarro-Oliveira *et al.* 2000). In addition, we observed a different effect of 8-week crowding on adrenergic constriction of the femoral artery in normotensive Wistar and WKY rats. While crowding resulted in elevated NA-induced vasoconstriction in Wistar rats (Bernatova *et al.* 2007a), WKY rats showed slightly impaired adrenergic vasoconstriction (Puzserova *et al.* 2006). Reduced NA-induced vasoconstriction in

crowded WKY rats may result either from functional down-regulation of α-adrenoceptors or from the elevated basal NO synthesis (Puzserova *et al.* 2006). Interestingly, in young female rats the exposure to 2-week crowding stress significantly impaired contraction to NA only in BHR but not in WKY and SHR (Slezak *et al.* 2014). Similar results were obtained by Fuchs *et al.* (1998), when the exposure to 10 days of behavioral stress decreased phenylephrine-induced (α-adrenoceptor-mediated) contraction in BHR rats, but not in WKY rats. On the other hand, 5 weeks of unpredictable stress increased the *in vitro* α-adrenoceptor-mediated constrictor response of the aorta in SD rats which was related to deficiency in NO production (Neves *et al.* 2009). Similarly, chronic stress increased neurogenic contractions of the superior mesenteric artery elicited by electrical stimulation of perivascular sympathetic nerve endings and significantly elevated vasoconstriction induced by exogenous NA, without modulation of BP and HR (Puzserova *et al.* 2012).

Altogether, abovementioned studies suggest that the duration of the stress stimulus, strain, sex and age considerably modify the NO-SNS interaction in stressful conditions.

NO and HPA axis interaction in stress

Regulation of the stress systems is extremely complex and occurs at multiple levels. After the exposure to stressor, sympathetic activation is followed by activation of HPA axis and elevated secretion of CRH (from the hypothalamus), ACTH (from the anterior pituitary) and glucocorticoids (from the adrenal cortex, in humans mainly cortisol, in rats mainly corticosterone).

Under acute stressful conditions, the negative feedback mechanism maintains the homeostasis of HPA axis. On the other hand, chronic stress-induced hyperactivity of HPA axis results in persistently elevated glucocorticoids (GC) levels (Zhu *et al.* 2014). The elevated GC reach various regions of the brain including hippocampus, hypothalamus, pituitary, etc. (Zhu *et al.* 2014). Glucocorticoids have a significant role in the metabolic response, mobilization of energetic sources and brain function (McEwen 2007). In addition, GC may affect both central mechanisms of BP regulation and vascular function. Hypertension is a prominent feature in patients with Cushing´s syndrome characterized by an excess of systemic GC (Peppa *et al.* 2011). It is also well known that hypertension is the major cardiovascular side effect of systemically administered GC (Walker and Edwards 1994). However, a variety of mechanisms have been proposed to explain exogenous and endogenous GC-induced hypertension (Peppa *et al.* 2011, Goodwin and Geller 2012).

NO is also a critical neurotransmitter and biological mediator of the neuroendocrine axis. NO-dependent control of central links of the stress reaction is supported by the fact that the pituitary gland receives a rich NO-ergic innervation (NOS-containing neurons) from the hypothalamus, including the paraventricular and supraoptic nuclei, suggesting regulatory role of NO not only in HPA axis but also in the posterior lobe of the pituitary (Vanhatalo and Soinila 1995).

NO is an important factor controlling CRH and ACTH release (Karanth *et al.* 1993, Lee *et al.* 1999, Rivier 2001). It is involved in central stimulation of the HPA axis by α_1- and α_2-adrenergic receptor agonists, and in mediation of the stimulatory action of these agonists on ACTH and GC secretion (Bugajski *et al.* 1999b). A significant increase of NOS activity and nNOS mRNA expression in the anterior pituitary was observed in rats exposed to acute immobilization as compared to non-stressed control rats (Kishimoto *et al.* 1996). Moreover, Karanth *et al.* (1993) showed that interleukin-2 activates CRH release from the hypothalamus by increasing NO production in which constitutive NOS is involved. Blockade of NO formation with L-NAME significantly blunted the ACTH response to stressors, suggesting that endogenous NO may exert a stimulatory effect on the circuitries leading to increased plasma ACTH levels during stress (Rivier 1994). On the other hand, the agonists of muscarinic and nicotinic acetylcholine receptors, carbachol and nicotine, increased plasma levels of ACTH and corticosterone in rats, and this effect was potentiated by NOS inhibitors (Gadek-Michalska and Bugajski 2005, Bugajski *et al.* 2006). Bugajski *et al.* (2006) found that NO significantly impairs the carbachol-induced HPA axis activation in rats under basal and social stress conditions. The same research group also demonstrated that NO acts as an inhibitory modulator of ACTH and corticosterone secretion in vasopressin-induced HPA axis activation in control and stressed rats (Bugajski *et al.* 1999a).

Moreover, NO is also important in the control of GC release. Tsuchiya *et al.* (1997) demonstrated that acute immobilization-induced increase of NO synthesis in the adrenal cortex can modify the stress-induced

corticosterone response to facilitate the recovery from the elevated corticosterone secretion by stress in the adrenal cortex to the resting basal level. In addition, an increase of NOS activity and up-regulation of nNOS mRNA expression in adrenal cortex was detected by Kishimoto *et al.* (1996) after a short immobilization stress. Similarly, in male Wistar rats the acute restraint stress markedly elevated pCort levels which were attenuated by pretreatment with L-arginine, a substrate for NO synthesis, but not by NOS inhibitor (L-NAME or 7-NI) pretreatment (Gulati *et al.* 2006). Moreover, stress gastric ulcers were attenuated by L-arginine and aggravated by L-NAME (Gulati *et al.* 2006). In the adrenal glands, elevated NO production was observed after acute immobilization, unaltered values after 4 and 9 days of stress and reduction of NO production was present after 14 days of stress exposure (Leza *et al.* 1998). In our studies, 8-week crowding had no effect on pituitary NOS activity in adult male Wistar and Wistar-mothered BHR rats, however elevated NOS activity was determined in the adrenal glands (Bernatova 2006, Bernatova *et al.* 2007a). In addition, different effects of stress on NO production were observed in other rats with a positive family history of hypertension (Bernatova 2006). Unchanged NOS activity was found in the pituitary and adrenal glands in male SHR-mothered BHR after 8-week crowding. However, in SHR, reduced NOS activity in the pituitary and unchanged NOS activity in the adrenal glands were found after the exposure to the same stressor (Bernatova 2006). Thus, it seems that alterations in NO production in the individual parts of the SNS and HPA axis during stress depend on the duration of stressor as well as on the genetic predispositions of experimental subjects.

Long-term stress may result in partial attenuation of stress-induced GC release as compared with acute or short-term stimuli. Habituation to stress is a normal response, since without physiological compensation there could be escalating detrimental effects on the organism. Indeed, for repeated restraint stress (Chen and Herbert 1995, Bauer *et al.* 2001), social stress (Chung *et al.* 1999), noise stress (Armario *et al.* 1986) and forced swimming (Cox *et al.* 1985) there is a habituation of GC responses. Similarly, an attenuation of corticosterone response was observed in mice exposed to chronic shaker stress, although there was still a more than 4-fold increase in pCort compared to controls (Bernatova *et al.* 2002a). However, in contrast to mice, a study in rats showed no attenuation of the pCort response to repeated shaker stress (Hashiguchi *et al.* 1997).

It also seems that NO is a crucial mediator in HPA axis regulation under chronic stress. Although acute GC elevation in the hippocampus and hypothalamus exerted a negative regulation of HPA axis, chronic GC elevation in the hippocampus, but not in the hypothalamus, accounted for chronic stress-induced hyperactivity of HPA axis due to impairment of its negative feedback regulation. GC activate the mineralocorticoid receptor (MR)-nNOS-NO pathway which results in the disruption of glucocorticoid receptors (GR) expression in the hippocampus, finally inducing HPA axis hyperactivity (Zhu *et al.* 2014). Therefore, NO produced by nNOS in the hippocampus is crucial in chronic stress and GC-induced hyperactivity of HPA axis (Zhou *et al.* 2011, Zhu *et al.* 2014). Thus, NO is an important regulator of HPA axis, which seems to be involved in both its activation and attenuation.

In our studies, 2-week crowding elevated pCort and systolic BP in SHR-mothered BHR of both sexes and male SHR while only mild pCort effect was observed in WKY and female SHR (Slezak *et al.* 2014, Bernatova *et al.* 2015). Interestingly, in our study pCort remained elevated, whereas NOS activity in the hypothalamus, cerebellum and brainstem remained decreased two weeks after cessation of chronic crowding stress in young BHR males (Bernatova *et al.* 2015). Persisting increase of pCort after cessation of stress may result from epigenetic mechanisms such as DNA methylation of GR (Turecki and Meaney 2016) which may deteriorate negative feedback regulation of HPA axis.

In experimental studies, Bechtold *et al.* (2009) found that endogenous corticosterone may act also *via* hindbrain GR to enhance the pressor response to stress in adult male BHR, but it promotes the adaptation in WKY rats. Subsequently, long-term GC overload may reduce expression and activity of individual NOS isoforms in various brain areas as well as in the cardiovascular system. Furthermore, it has been shown that GC led to alterations in neuronal NO release in the CNS, which is an important mechanism in hypertension development (Goodwin and Geller 2012).

In the vasculature, GC receptors are present on the endothelium and vascular smooth muscle cells (Provencher *et al.* 1995, Ray *et al.* 1997, Rogers *et al.* 2002). Glucocorticoids can act as modulators of both vascular smooth muscle and endothelial functions (Goodwin and Geller 2012). GC were shown to support

vasoconstriction as they increase the response to NA, angiotensin II and other vasoconstrictors (Grunfeld *et al.* 1985, Walker and Edwards 1994, Saruta 1996, Ullian 1999, Peppa *et al.* 2011). Saruta (1996) found that the number of AT_1 receptors of vascular smooth muscle cells is significantly increased by GC. Moreover, increased synthesis and secretion of endothelin-1 (the strongest vasoconstrictor), increased vascular smooth muscle cytosolic calcium levels, increased synthesis of catecholamines and β_1-adrenergic receptor expression, increased availability of α_1-adrenergic receptors on vascular smooth muscles, enhanced synthesis and action of neuropeptide Y and vasopressin and the activation of RAS were found to be pathogenetically involved in the corticosteroid-induced hypertension (Peppa *et al.* 2011). In addition, Falardeau and Martineau (1989) found that GC-induced hypertension is associated with an inhibition of prostacyclin biosynthesis and an alteration of its metabolism. Furthermore, Molnar *et al.* (2008) suggested that GC may contribute to vascular disease also *via* MR signaling.

Glucocorticoids were also shown to participate in the regulation of vascular NO production. The inhibitory effect of GC on eNOS expression and NOx production was observed in cultured bovine coronary artery and aortic endothelial cells as well as in human umbilical vein endothelial cells (Wallerath *et al.* 1999, Rogers *et al.* 2002). Incubation of cultured human umbilical vein endothelial cells or bovine aortic endothelial cells with dexamethasone (synthetic glucocorticoid) reduced eNOS mRNA and protein expression, an effect that was prevented by the GR antagonist mifepristone (Wallerath *et al.* 1999). Moreover, BP increase, plasma NOx (an indicator of total body NO synthesis) decrease together with the down-regulated expression of eNOS were found in the aorta and several other tissues of GC-treated rats (Wallerath *et al.* 1999). Rogers *et al.* (2002) demonstrated that cortisol, *via* activation of GR, suppresses NOx release in cultured bovine coronary artery endothelial cells by down-regulation of eNOS proteins and inhibition of intracellular Ca^{2+} mobilization. Furthermore, Simmons *et al.* (1996) found that GC inhibited NO production by iNOS in cardiac microvascular endothelial cells following cytokine exposure and this was mediated by limiting a NOS cofactor tetrahydrobiopterin (BH_4) and NOS substrate L-arginine availability. Mitchell *et al.* (2004) showed that dexamethasone *via* GR-mediated decrease of guanosine triphosphate cyclohydrolase I (GTPCH1 – the rate-limiting enzyme for the *de novo* synthesis of BH_4) mRNA expression and GTPCH1 down-regulation contributes to GC-induced reduction of endothelium-dependent relaxation in the isolated rat aorta. Moreover, GC responsive elements in the eNOS gene promoter region were demonstrated by Liu *et al.* (2009). These studies suggested that the primary mechanism of GC-induced hypertension may result rather from the GC action on the vascular tissues than from excessive sodium and water reabsorption after the activation of renal MR-associated mechanism (Goodwin *et al.* 2011, Goodwin and Geller 2012).

In vivo studies demonstrated that dexamethasone increased MAP in wild-type C57 Bl6 mice ($eNOS^{+/+}$ mice), but had no effect on BP in $eNOS^{-/-}$ mice derived from the same strain (Wallerath *et al.* 2004). The authors concluded that the expressional down-regulation of eNOS and the ensuing reduction of vascular NO production contributes to hypertension caused by GC. Goodwin *et al.* (2011) found that knock-out of the vascular endothelial GR abrogates dexamethasone-induced hypertension. Moreover, dexamethasone reduced neuronal NO release from the perivascular innervation of the mesenteric arteries in SHR but not WKY rats (Aras-Lopez *et al.* 2009), which also proves an important role of GC in development of stress-induced hypertension in predisposed subjects. GC were also shown to increase oxidative stress (Duckles and Miller 2010), which seems to play an important role in the development of endothelial dysfunction as mentioned above. Thus GC may alter NO release from the endothelium, CNS and perivascular nervous system. In addition, corticosteroid-induced metabolic abnormalities, such as hyperglycemia, excess liberation of free fatty acids, increased plasma levels of triglycerides, insulin resistance and hyperinsulinemia exert pathological impact on endothelial function and appear to contribute to the corticosteroid-induced hypertension (Peppa *et al.* 2011, Zhang *et al.* 2012).

Above mentioned findings support the theory that GC affect the vascular smooth muscle cells and endothelium, induce the imbalance between vasoconstriction and vasorelaxation, favoring vasoconstriction, and resulting in the increase of systemic vascular resistance and BP increase.

Oxytocin and vasopressin

Hormones of the posterior pituitary, oxytocin

(OT) and vasopressin (VP), represent an important component of the stress response (Jezova *et al.* 1995, Ondrejcakova *et al.* 2010, Danevova *et al.* 2013, Babic *et al.* 2015). OT and VP are involved in the regulation of BP and other cardiovascular functions (Gutkowska *et al.* 2000). There are studies showing that OT and VP are involved in the pressor and HR responses to stressors (Callahan *et al.* 1992, Morris *et al.* 1995, Bernatova *et al.* 2004, Ondrejcakova *et al.* 2010). There was a sustained reduction of BP in OT knock-out (OTKO) mice at rest, while accentuated BP responses were observed in chronic stress (Bernatova *et al.* 2004). Wsół and colleagues reported that central application of an OT receptor antagonist enhanced BP and HR increases elicited by environmental stress (Wsół *et al.* 2008, Wsół *et al.* 2009). In addition, simulated stress-induced oxytocin secretion by chronic treatment with oxytocin *via* osmotic minipumps led to reduced pressor response to α_1-adrenergic receptor agonist (Ondrejcakova *et al.* 2010). These studies provide the evidence that OT may play a role in the attenuation of stress-induced pressor response.

Concerning the interaction of NO and neurohypophysial hormones, several studies emphasized the inhibitory action of centrally produced NO on the secretion of OT and VP hormones (Stern and Ludwig 2001, Reis *et al.* 2007) (Fig. 2). However, Wangensteen *et al.* (2003) reported that the administration of nNOS inhibitor 7-NI to normal rats produced a mild polyuria-polydipsia syndrome, which has been attributed to an inhibitory effect of 7-NI on VP release. Moreover, in chronic L-NAME-treated rats, plasma VP levels have been reported to be unchanged (Liu *et al.* 1998). Rettori *et al.* (1997) showed that OT stimulates NOS in the hypothalamus *via* NA, resulting in an increased NO release. Furthermore, the released NO can act back on oxytocinergic terminals to suppress the release of OT in an ultrashort-loop negative feedback. With regard to the HPA axis, there was a reduction of stress-induced corticosterone release in chronically stressed OTKO mice (Bernatova *et al.* 2004). This fits with findings of Gibbs (1985) who observed a reduction in stress-induced ACTH levels when OT was neutralized with specific antisera. Data suggest that OT accentuates ACTH-dependent GC release. On the other hand, VP has only a weak ability to upregulate the ACTH secretion, but it markedly potentiates the effects of CRH (Oshikawa *et al.* 2004), suggesting its role in upstream regulation of HPA axis. Both hormones, OT and VP, were shown to interact to each other and with the HPA axis and thus supposedly contribute to BP regulation under stress conditions.

In addition, OT synthesis and OT receptors (OTR) were also proved in the heart and large vessels (Gutkowska *et al.* 2000). Miller *et al.* (2002) have demonstrated the presence of OTR in the small resistance arteries. Therefore, OT (including locally produced peptide) may have important regulatory functions in the heart and vasculature, including negative chronotropic effect on the heart and the regulation of local vascular tone *via* stimulation of NO-cGMP pathway (Thibonnier *et al.* 1999, Gutkowska *et al.* 2000). Experiments with primary cultures of human endothelial cells revealed that these cells express OTR and their stimulation by OT produced mobilization of intracellular Ca^{2+} and the release of NO (Thibonnier *et al.* 1999).

However, the studies investigating effect of OT on vascular function produced ambiguous results. High concentrations of OT induced renal vasoconstriction in the rats by activating vasopressin V_{1A} receptors (Loichot *et al.* 2001). Both OT and VP caused endothelium-dependent relaxation in the isolated canine basilar artery by activating V_1 receptors, in contrast to the femoral artery, in which these hormones caused endothelium-independent contractions (Katusic *et al.* 1986). Using a wire myograph system, Miller *et al.* (2002), showed that OT failed to produce vasorelaxation in the preconstricted small mesenteric arteries, uterine arcuate arteries and thoracic aorta from nonpregnant and pregnant rats, and high concentrations of OT caused V_{1A}-receptor-mediated vasoconstriction. These findings reflect the marked variation of responses to OT and VP in different vascular beds. Thus, despite the fact that vascular endothelial cells express OTR, the involvement of OT/OTR/NO system in modulation of vascular resistance and BP in stress is still unclear.

Thus, the exact OT and VP action in BP regulation and their relationships with NO in the brain and cardiovascular system during stress needs further examination.

NO involvement in BP regulation during stress

NO is recognized as an important signaling molecule in the CNS and periphery, and this includes a significant influence on the activity of stress systems (Fig. 2). After the exposure to stressor the SNS activation is followed by the activation of its sympathoadreno-

medullary part and RAS, which is followed by elevation of ROS, alterations in endothelial function and decrease of endothelial NO (eNO) bioavailability, which collectively results in the elevation of BP. Regarding the SNS activity, there is no consensus on the opposing actions of NO produced in different brain regions on SNS activity. Several studies suggested that NO reduces sympathetic output to the peripheral tissues. In chronic stress the effect of neuronal NO (nNO) on the SNS activity (mainly on the central sympathetic outflow) remain unresolved. However, an increase in the sympathetic influences to the peripheral vessels (resulting in reduced eNO bioavailability), participates in the development and progression of the hypertensive state.

Meanwhile, the activation of HPA axis, in which nNO seems to be important, leads to increased release of GC. In acute (or short-term) stress, GC increase mediates the attenuation of HPA activity. In the hypothalamus, NO contributes to the negative control of HPA axis activity (Mancuso *et al.* 2010). In the hippocampus nNOS-derived NO is an important molecule in the development of HPA axis hyperactivity during chronic stress (Zhu *et al.* 2014). Thus NO exerts both stimulatory and inhibitory effect within the HPA-axis depending on the brain area. In addition, NO produced in the adrenal cortex may inhibit GC release in stressed conditions. Our results showed that in chronic stress reduced NO in the selected brain areas was associated with high activity of HPA axis and elevated BP in prehypertensive rats. It is also evident that chronically elevated GC can cause hypertension by acting on the endothelium, in which reduces eNO bioavailability.

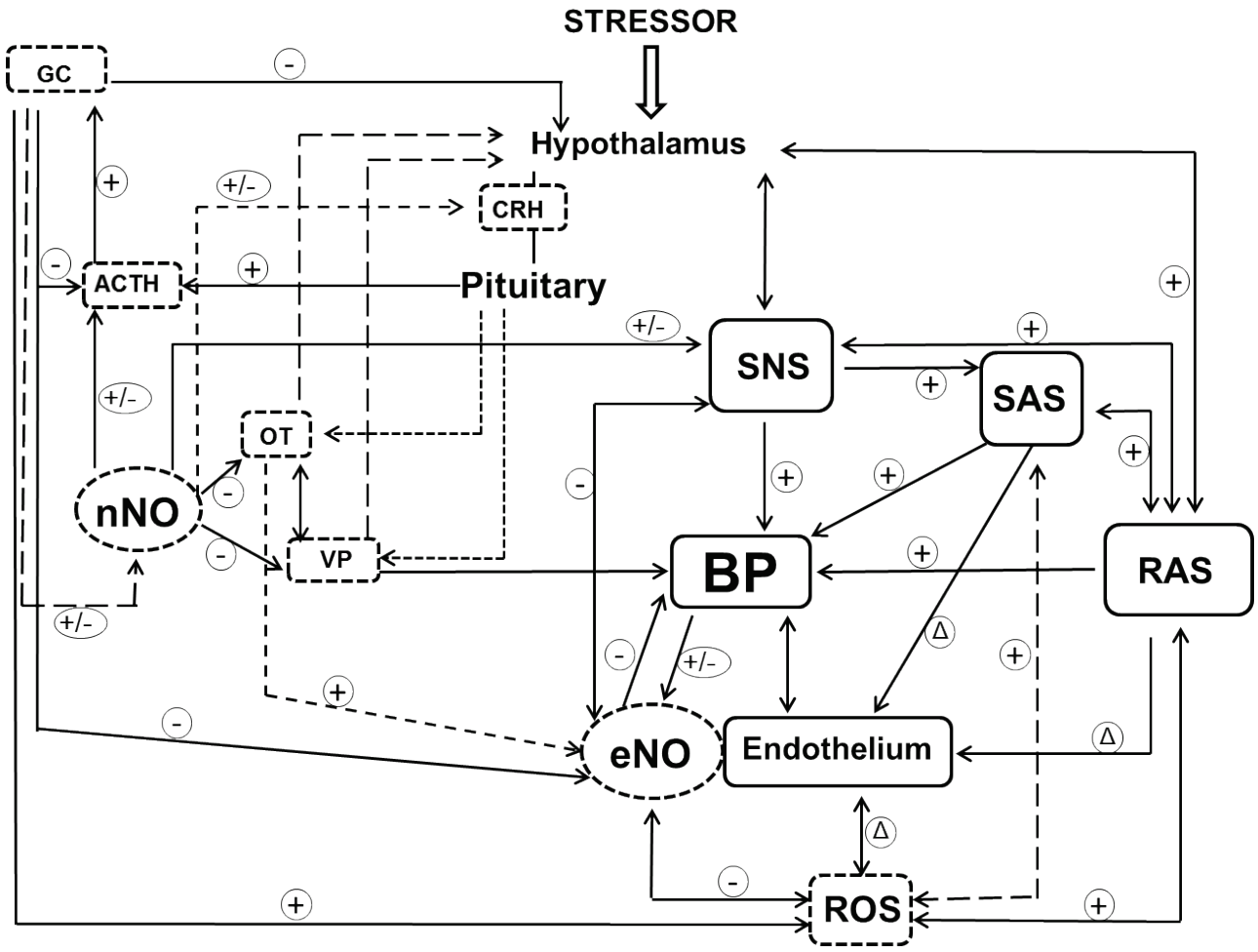

Fig. 2. A simplified scheme of nitric oxide involvement in the main blood pressure regulatory mechanisms in stress. Inhibiting effects are marked by "minus" mark, activating effects are marked by "plus" mark. The alterations in endothelial function (including those other than NO-mediated) are marked by Δ. ACTH – adrenocorticotropic hormone, BP – blood pressure, CRH – corticotropin releasing hormone, eNO – nitric oxide synthesized by endothelial nitric oxide synthase, GC – glucocorticoids, nNO – nitric oxide synthesized by neuronal nitric oxide synthase, NO – nitric oxide, OT – oxytocin, RAS – renin-angiotensin system, ROS – reactive oxygen species, SAS – sympathoadrenomedullary system, SNS – sympathetic nervous system, VP – vasopressin.

OT and VP were shown to interact to each other and with the HPA axis and supposedly to contribute to BP regulation under stress conditions. Concerning the interaction of NO and neurohypophysial hormones, several studies emphasize the inhibitory action of centrally produced NO on the secretion of OT and VP hormones. However, the exact BP regulation associated with the OT and VP action and their relationships with NO in the brain and CVS during stress remain largely unexplored.

Of course, Figure 2 is not exhausting scheme of BP regulation in stress. Other regulatory mechanisms, the involvement of which is variable in the course of stress, are also involved, and not all of them are satisfactorily elucidated by now. Together, these mechanisms create a very complex network of mutual regulations and feedbacks, in which failure of one mechanism can be compensated by the other one. Yet long-term SNS activation and dysregulation of HPA axis during chronic and repeated exposure to stressors may destroy this precise network leading to hypertension development. Although the role of endogenous NO in regulation of the activity of HPA axis and SNS remains controversial, a large body of evidence demonstrates that BP regulation in stress closely depends on the interactions among NO and stress systems.

Conclusions

All the above mentioned studies suggest that the effect of stress on BP and vascular function depends on genetic predisposition to hypertension, duration of stress, age and sex. NO production in the various parts of the HPA axis, SNS and the vasculature may be considerably altered in response to diverse stressors affecting the release of various hormones and autacoids. Despite many discrepancies and contradictions, elevated NO synthesis, especially in the initial phase of stress may be considered a stress-limiting mechanism, facilitating the recovery from stress to the resting levels *via* attenuation of both GC release and SNS activity as well as by increased NO-dependent vasorelaxation. On the other hand, reduced levels of NO were observed in the later phases of stress and in subjects with genetic predisposition to hypertension, irrespectively, in which reduced NO bioavailability may account for disruption of NO-mediated BP regulatory mechanisms and accentuated SNS and GC effects. Thus NO plays a crucial role in the regulation of the stress systems and thereby in the BP regulation in stress.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

ACh – acetylcholine
ACTH – adrenocorticotropic hormone
AT_1 – angiotensin II type 1 receptor
BH_4 – tetrahydrobiopterin
cGMP – cyclic guanosine monophosphate
CNS – central nervous system
COX – cyclooxygenase
CRH – corticotropin releasing hormone
CVDs – cardiovascular diseases
CVS – cardiovascular system
EDCFs – endothelium-derived contracting factors
EDHFs – endothelium-derived hyperpolarizing factors
EDRFs – endothelium-derived relaxing factors
eNO – nitric oxide synthesized by eNOS
eNOS – endothelial nitric oxide synthase
GABA – gamma-aminobutyric acid
GC – glucocorticoids
GR – glucocorticoid receptors
GTPCH1 – guanosine triphosphate cyclohydrolase I
HPA – hypothalamic-pituitary-adrenocortical
HR – heart rate
iNOS – inducible nitric oxide synthase
L-NAME – N^G-nitro-L-arginine methyl ester
MAP – mean arterial pressure
MR – mineralocorticoid receptor
NA – noradrenaline
NMDA – N-methyl-D-aspartate

nNO – nitric oxide synthesized by nNOS
nNOS – neuronal nitric oxide synthase
NO – nitric oxide
NOS – nitric oxide synthase
NOx – nitrate/nitrite (stable NO metabolites)
NTS – nucleus tractus solitarii
OT – oxytocin
OTKO – oxytocin knock-out
OTR – oxytocin receptor
pCort – plasma corticosterone
PGI_2 – prostacyclin
PVN – paraventricular nucleus
RAS – renin-angiotensin system
ROS – reactive oxygen species
RVLM – rostral ventrolateral medulla
SAS – sympathoadrenomedullary system
SD – Sprague-Dawley rats
SHR – spontaneously hypertensive rats
SNS – sympathetic nervous system
VP – vasopressin
WKY – Wistar-Kyoto rats
7-NI – 7-nitroindazole

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