MINIREVIEW

The Organ-Specific Nitric Oxide Synthase Activity in the Interaction With Sympathetic Nerve Activity: A Hypothesis

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Summary

The sympathetic nerve activity (SNA) is augmented in hypertension. SNA is regulated by neuronal nitric oxide synthase (nNOS) or endothelial nitric oxide synthase (eNOS) activity in hypothalamic paraventricular nuclei (PVN) and/or brainstem rostral ventrolateral medulla. High nNOS or eNOS activity within these brain regions lowers the SNA, whereas low cerebral nNOS and/or eNOS activity causes SNA augmentation. We hypothesize that the decreased cerebral nNOS/eNOS activity, which allows the enhancement of SNA, leads to the augmentation of renal eNOS/nNOS activity. Similarly, when the cerebral nNOS/eNOS activity is increased and SNA is suppressed, the renal eNOS/nNOS activity is suppressed as well. The activation of endothelial α_2-adrenoceptors, may be a possible mechanism involved in the proposed regulation. Another possible mechanism might be based on nitric oxide, which acts as a neurotransmitter that tonically activates afferent renal nerves, leading to a decreased nNOS activity in PVN. Furthermore, the importance of the renal nNOS/eNOS activity during renal denervation is discussed. In conclusion, the presented hypothesis describes the dual organ-specific role of eNOS/nNOS activity in blood pressure regulation and suggests possible connection between cerebral NOS and renal NOS *via* activation or inhibition of SNA, which is an innovative idea in the concept of pathophysiology of hypertension.

Key words

Sympathetic nerve activity • Nitric oxide synthase activity • Hypertension • Kidney • Rostral ventrolateral medulla • Paraventricular nuclei

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Introduction

The activity of sympathetic nervous system (SNS) represents a principle blood pressure (BP) regulating mechanism. In various models of experimental hypertension the activity of SNS was enhanced (Osborn *et al.* 2005, Vavřínová *et al.* 2019). An important role in the long-term control of arterial pressure by sympathetic nerve activity (SNA) may involve baroreflex-independent mechanisms (Osborn *et al.* 2009). The neurophysiological studies of SNA showed that the regulation of SNA involves the inputs from insular and prefrontal cortices, amygdala, hypothalamic nuclei and rostral ventrolateral medulla (Barman and Yates 2017). On the other side, Guyton (1989) proposed that the SNS could chronically regulate arterial pressure *via* changes of the renal function curve. Thus, the long-term regulation of BP seems to be primary dependent on the stimuli exchange between SNA and the kidney.

The regulation of sympathetic nerve activity

Already 25 years ago it was observed that BP increased after injection of very low dose (0.3 mg/100g body weight) of nitric oxide synthase (NOS) inhibitor

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into the posterior hypothalamus (Gerová 2000, Gerová *et al.* 1995). Similarly, microinjection of NOS inhibitor into the paraventricular nuclei (PVN) elicited an increase in renal sympathetic nerve discharge, arterial blood pressure, and heart rate (Zhang *et al.* 1997). Recently, sympathoexcitation and BP increase was reported after the silencing of nNOS within the PVN of Wistar rats (McBryde *et al.* 2018), but 6 weeks of nNOS inhibitor application in drinking water did not alter systolic BP of Wistar rats (Cacanyiova *et al.* 2009). These results point to a dual organ-specific role of nNOS in BP regulation, which will be described in the proposed hypothesis.

Similarly as in PVN, it was shown that the regulation of SNA in rostral ventrolateral medulla (RVLM) is modulated by nitric oxide (NO) levels produced by NOS (Chan and Chan 2014). Low concentrations of NO derived from neuronal NOS (nNOS) or endothelial NOS (eNOS) in the RVLM lead to enhanced SNA (sympathoexcitation), whereas high concentrations of NO produced by the inducible NOS in the RVLM result in the impairment of SNA (sympathoinhibition) (Chan and Chan 2014). Similarly, sympathoinhibition was observed after the overexpression of eNOS in the RVLM, probably due to the increased concentration of NO (Kishi 2013). Other mechanisms may also alter NO levels in hypothalamus and brainstem, such as the uncoupling of eNOS under tetrahydrobiopterin (BH_4) deficiency, which converts eNOS to a superoxide-producing enzyme (Li and Förstermann 2013), or the interference with nNOS dimerization within the PVN (Rossi *et al.* 2010). Taken together, high cerebral nNOS or eNOS activity impairs the SNA, whereas low nNOS and/or eNOS activity causes SNA augmentation (Fig. 1).

Hypothesis

We hypothesized that the increased nNOS/eNOS activity in the brain structures causes the inhibition of SNA, which is leading to the inhibition of renal eNOS/nNOS activity (Fig. 1). Conversely, when the cerebral nNOS/eNOS activity is decreased, the SNA is enhanced and the renal eNOS/nNOS activity is enhanced as well. Thus, the NOS activity displays organ-specific alterations that are opposite in the brain and the kidney. Enhanced cerebral NOS activity lowers the renal NOS activity and *vice versa*. This connection is controlled by the activation or inhibition of SNA (Fig. 1).

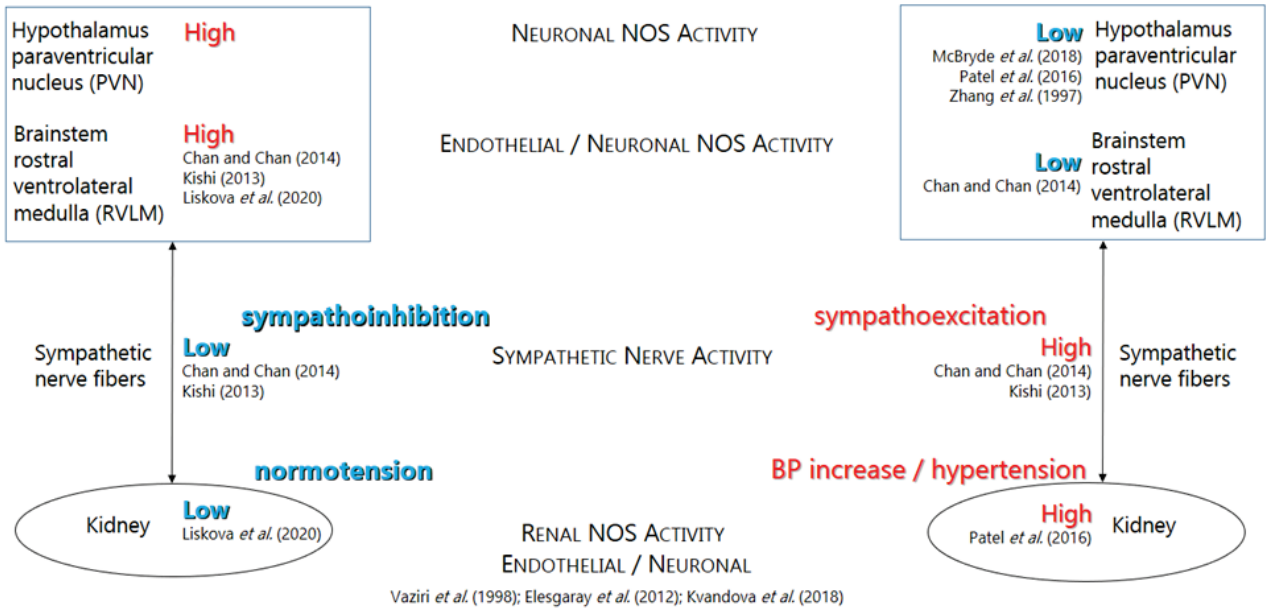

Fig. 1. Scheme of the dual organ-specific role of NOS activity involved in blood pressure (BP) regulation. The references of cited publications evaluating the corresponding nitric oxide synthase (NOS) activity and sympathetic nerve activity (SNA).

Renal nitric oxide synthase activity

It was shown that the L-Arg/NO pathway is activated before the onset of hypertension, because enhanced NO production and NOS activity in the kidney and aorta were reported already in 3-week-old spontaneously hypertensive rats (SHR) (Vaziri *et al.* 1998a). In both the renal cortex and renal medulla, the

NOS activity, the expression of eNOS and the nitrite and nitrate excretion were higher in SHR than in WKY (Elesgaray *et al.* 2012). The enhanced NOS activity in the kidney was also present in borderline hypertensive rats (BHR), which are the offspring of SHR mothers and Wistar-Kyoto fathers (Kvandova *et al.* 2018). NOS activity was higher in the renal cortex of SHR when compared to BHR, whereas BP of BHR animals was lower when compared to the SHR (Kvandova *et al.* 2018), suggesting that the enhanced renal NOS activity is not dependent on genetic predispositions, but it resembles to the difference in BP between BHR and SHR. It is of interest that the relaxing effect of exogenous NO donor, sodium nitroprusside, was higher in normotensive rats and L-arginine prevented the relaxing effect of sodium nitroprusside in renal arteries of normotensive rats more than in renal arteries of SHR (Orescanin and Milovanović 2006). As mentioned above, the enhanced renal NOS activity is well documented in animals with increased SNA, but to our knowledge, increased NOS activity in the brainstem and hypothalamus and decreased NOS activity in the kidney, were observed only in our study after the administration of ultra-small iron oxide nanoparticles (Líšková *et al.* 2020).

Mechanisms implicated in the hypothesis

According to our hypothesis, the enhanced SNA is accompanied by increased renal NOS activity (Fig. 1). One of possible mechanisms, which may be involved in the enhancement of renal NOS activity *via* SNA, represent the activation of endothelial α_2-adrenoceptors. It was documented that in periosteum arterioles of trained leg, noradrenaline released from sympathetic nerves activated the endothelial α_2-adrenoceptors resulting in NO release and sustained dilatation (Fukuta *et al.* 2019). Relationship between physical inactivity and SNA was proposed to cause changes in the RVLM, which contribute to chronic cardiovascular disease (Mischel *et al.* 2015). It remains to be determined whether the activation of NOS alter endothelial α_2-adrenoceptors in the kidney of hypertensive animals.

The organ-specific NOS activity proposed in this hypothesis would play a role after the renal denervation (RDN). RDN restored the nNOS in the PVN, which was decreased in rats with heart failure, on the other hand, the renal sympathetic overactivity in rats with heart failure reduced the expression of nNOS in the PVN (Patel *et al.* 2016). Patel *et al.* (2016) proposed that tonic activation of afferent renal nerves contributes to the activation of preautonomic PVN neurons during heart failure. These neural signals from the kidney may be tonically active in the heart failure and are abrogated by RDN (Patel *et al.* 2016). According to the proposed hypothesis, the enhanced renal eNOS/nNOS activity could lead to the tonic activation of afferent renal nerves leading to impaired nNOS within the PVN, because NO may act as a neurotransmitter involved in the activation of afferent renal nerves. Interestingly, it was reported that the NO-deficient hypertension may be at least partly dependent on the integrity of the renal nerves (Matsuoka *et al.* 1994).

Clinical trials investigating the possibility of renal denervation (RDN) as a potential treatment of resistant hypertension showed only partially successful results (Bhatt *et al.* 2014, Krum *et al.* 2009). One of the proposed reasons was the insufficiency of renal denervation (Chen *et al.* 2016). Sufficient RDN induces significant renal artery vasodilation which may serve as a possible indicator of successful renal sympathetic nerve damage during the RDN procedure (Chen *et al.* 2016). Furthermore, the renal vasodilation is a predictor of efficient BP response and positively correlates with systolic BP reduction and plasma norepinephrine decrease over three months after the renal nerve ablation (Chen *et al.* 2016). According to our hypothesis, the renal NOS activity could lead to the inhibition of nNOS expression in PVN or to the lowering of NOS activity in RVLM *via* preserved nerve fibers even after incomplete RDN. On the other hand, successful RDN would allow the augmented renal NOS activity to produce NO without the sympathetic nerve fiber feedback leading to vasodilation and BP reduction. BP reduction after RDN was reported in several clinical trials (Azizi *et al.* 2015, Krum *et al.* 2009), but the role of NOS activity was not evaluated.

During renal ischemia, NO is involved in the maintenance of kidney function and the inhibition of NO synthase enhanced the kidney sensitivity to damage in Inactin (thiobutabarbital)-anaesthetized rats (Chintala *et al.* 1993). Conversely, in well-trained conscious rabbits the renal SNA was decreased after the *i.v.* administration of NOS inhibitor (N^{ω}-nitro-L-arginine methyl ester, L-NAME), although BP was increased (Liu *et al.* 1998). Similar decrease in renal SNA after NOS inhibition was observed during a background infusion of angiotensin II and phenylephrine (Liu *et al.* 1998). The decrease in renal SNA despite the BP rise is in agreement with proposed

hypothesis that the inhibition of renal NOS lead to the enhancement of cerebral NOS activity (in PVN or RVLM) and inhibition of renal SNA. The elevation of BP can be explained *via* an increase in peripheral resistance after NOS inhibition. Although the above mentioned studies support the hypothesis of dual organ-specific role of NOS, studies specifically designed to investigate the renal NOS activity and/or NO bioavailability together with the recording of renal SNA are needed to exactly evaluate the proposed hypothesis.

The relationship between NO and other important regulatory mechanisms such as vasopressin, angiotensin II, endothelin-1, atrial natriuretic peptide *etc.* which was investigated under various pathological conditions, clearly points to the important role of NO in the regulation of renal blood flow and glomerular filtration rate.

Implication of the presented hypothesis under the conditions of chronic renal failure

In chronic renal failure, plasma NO concentration was reduced that was reversed by exogenously supplied L-arginine. The treatment with captopril administered in combination with L-arginine prevented chronic renal failure (Ashab *et al.* 1995). It was suggested that the beneficial effect of captopril is mediated through a specific L-arginine/NO pathway (Ashab *et al.* 1995). It is of interest that the deletion of AT_1 receptors is coupled to enhanced nNOS protein expression in renal microvascular and tubular structures and may provide an enhanced ability of the kidney to generate NO (Park and Harrison-Bernard 2008). The elevated levels of angiotensin II are present under anesthesia (Faber 1989). The increase in circulating angiotensin II is critical for the sympathoexcitation induced by NOS inhibition in anaesthetized animals and this may explain the difference between results obtained from conscious and anaesthetized animals (Liu *et al.* 1998).

I.v. application of NOS inhibitor did not change the BP in conscious 5/6 nephrectomized rats (Drábková *et al.* 2020). Renal afferent signals cause a reflex increase of sympathetic outflow from the posterior and lateral hypothalamic nuclei and the locus ceruleus of 5/6 nephrectomized rats through the activation of noradrenergic neurons resulting in blood pressure rise in rats with chronic renal insufficiency (Campese and Kogosov 1995). Increased afferent signals from the kidneys may cause reflex increases in efferent sympathetic nervous system activity (Campese and Kogosov 1995). In the nephrons of rats with subtotal nephrectomy fed high-NaCl diet, the tubuloglomerular feedback response becomes anomalous due to exaggerated NO response (Thomson 2019). Contrary to these observations there are measurements in 5/6 nephrectomized rats under general anesthesia with pentobarbital sodium (50 mg/kg *i.p.*), where the reduction in urinary excretion of stable NO metabolites as well as depressed NOS activity and decreased eNOS protein contents in the remnant kidney were observed in animals with chronic renal failure (Vaziri *et al.* 1998b). Similarly, under general anesthesia with thiopental (50 mg/kg *i.p.*), the levels of stable NO metabolites as well as the expression of eNOS proteins were decreased in the kidney of rats with chronic renal failure (Kim *et al.* 2000).

It is well known that certain types of anesthesia lead to sympathetic inhibition (Bencze *et al.* 2013). Considering the above mentioned studies involved in chronic renal failure evaluation, it is possible that anesthesia lead to renal NOS activity inhibition as well as to SNA inhibition. In context of the proposed hypothesis, the decrease in SNA would lead to a decrease in renal NOS activity, or the decreased renal NOS would lead to the augmentation of cerebral NOS activity and decrease in the SNA.

Conclusions

In conclusion, the presented hypothesis suggests the dual role of NOS in the regulation of BP, which is new in the concept of pathophysiology of hypertension. Augmented renal NOS activity contributes *via* afferent renal nerves to impaired NOS activity in BP regulatory brain regions, thus further increasing sympathetic outflow. The augmented renal NOS activity under hypertensive conditions is not sufficient to oppose the excessive SNA, but the increase in NO levels causes a reduction in the sensitivity of vascular smooth muscle cells of renal arteries to NO, resulting in a further decrease of the vasodilatation. Presented mechanism may partially complement the baroreflex in the regulation of blood pressure. In contrast to baroreflex, where the regulation is rather fast, the cerebral-renal feedback regulation of NOS activity is slower. If this hypothesis is correct, then the renal NOS activity, which mirrors the changes of SNA, may be a part of a protecting

mechanism to preserve SNA after activation of NO-dependent relaxation pathway. However, under the chronic stimulation of SNA, the same mechanism could be at least partially involved in hypertension development.

Conflict of Interest

There is no conflict of interest.

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