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 α2-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

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
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 (BH₄) 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).

**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

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**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).

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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 arterial arteries of normotensive rats more than in arterial 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 (Lišková 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 α2-adrenoceptors. It was documented that in periosteum arterioles of trained leg, noradrenaline released from sympathetic nerves activated the endothelial α2-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 α2-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 (Nω-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 AT1 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.

**References**

ASHAB I, PEER G, BLUM M, WOLLMAN Y, CHERNIHOVSKY T, HASSNER A, SCHWARTZ D, CABILI S, SILVERBERG D, IAINA A: Oral administration of L-arginine and captopril in rats prevents chronic renal failure by nitric oxide production. Kidney Int 47: 1515-1521, 1995. [https://doi.org/10.1038/ki.1995.214](https://doi.org/10.1038/ki.1995.214)

AZIZI M, SAPOVAL M, GOSSE P, MONGE M, BOBRIE G, DELSART P, MIDULLA M, MOUNIER-VÉHIER C, COURAND PY, LANTELME P, DENOLLE T, DOURMAP-COLLAS C, TRILLAUD H, PEREIRA H, PLOUIN P-F, CHATELLIER G: Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet 385: 1957-1965, 2015. [https://doi.org/10.1016/S0140-6736(14)61942-5](https://doi.org/10.1016/S0140-6736(14)61942-5)

BARMAN SM, YATES BJ: Deciphering the neural control of sympathetic nerve activity: status report and directions for future research. Front Neurosci 11: 730, 2017. [https://doi.org/10.3389/fnins.2017.00730](https://doi.org/10.3389/fnins.2017.00730)

BENCZE M, BEHULIAK M, ZICHA J: The impact of four different classes of anesthetics on the mechanisms of blood pressure regulation in normotensive and spontaneously hypertensive rats. Physiol Res 62: 471-478, 2013. [https://doi.org/10.33549/physiolres.932637](https://doi.org/10.33549/physiolres.932637)

BHATT DL, KANDZARI DE, ONEILL WW, D’AGOSTINO R, FLACK JM, KATZEN BT, LEON MB, LIU M, MAURI L, NEGOTA M, COHEN SA, OAPARIL S, ROCHA-SINGH K, TOWNSEND RR, BAKRIS GL: A controlled trial of renal denervation for resistant hypertension. N Engl J Med 370: 1393-1401, 2014. [https://doi.org/10.1056/NEJMoa1402670](https://doi.org/10.1056/NEJMoa1402670)

CACANYIOVA S, KRISTEK F, GERVAKOVA M, KRENEK P, KLIMAS J: Effect of chronic nNOS inhibition on blood pressure, vasoactivity, and arterial wall structure in Wistar rats. Nitric Oxide 20: 304-310, 2009. [https://doi.org/10.1016/j.niox.2009.03.002](https://doi.org/10.1016/j.niox.2009.03.002)

CAMPESE VM, KOGOSOV E: Renal afferent denervation prevents hypertension in rats with chronic renal failure. Hypertension 25: 878-882, 1995. [https://doi.org/10.1161/01.HYP.25.4.878](https://doi.org/10.1161/01.HYP.25.4.878)

CHAN SH, CHAN JY: Brain stem NOS and ROS in neural mechanisms of hypertension. Antioxid Redox Signal 20: 146-163, 2014. [https://doi.org/10.1089/ars.2013.5230](https://doi.org/10.1089/ars.2013.5230)

CHEN W, DU H, LU J, LING Z, LONG Y, XU Y, XIAO P, GYAWALI L, WOO K, YIN Y, ZRENNER B: Renal artery vasodilation may be an indicator of successful sympathetic nerve damage during renal denervation procedure. Sci Rep 6: 37218, 2016. [https://doi.org/10.1038/srep37218](https://doi.org/10.1038/srep37218)

CHINTALA MS, CHIU PJ, VEMULAPALLI S, WATKINS RW, SYBERTZ EJ: Inhibition of endothelial derived relaxing factor (EDRF) aggravates ischemic acute renal failure in anesthetized rats. Naunyn Schmiedebergs Arch Pharmacol 348: 305-310, 1993. [https://doi.org/10.1007/BF00169160](https://doi.org/10.1007/BF00169160)

DRÁBKOVÁ N, HOJNÁ S, ZICHA J, VANĚČKOVÁ I: Contribution of selected vasoactive systems to blood pressure regulation in two models of chronic kidney disease. Physiol Res 69: 405-414, 2020. [https://doi.org/10.33549/physiolres.934392](https://doi.org/10.33549/physiolres.934392)

ELEGARAY R, CANIFFI C, SAVIGNANO L, ROMERO M, MAC LAUGHLIN M, ARRANZ C, COSTA MA: Renal actions of atrial natriuretic peptide in spontaneously hypertensive rats: the role of nitric oxide as a key mediator. Am J Physiol Renal Physiol 302: F1385-F1394, 2012. [https://doi.org/10.1152/ajprenal.00624.2011](https://doi.org/10.1152/ajprenal.00624.2011)

FABER JE: Effects of althesin and urethan-chloralose on neurohumoral cardiovascular regulation. Am J Physiol 256: R757-R765, 1989. [https://doi.org/10.1152/ajpregu.1989.256.3.R757](https://doi.org/10.1152/ajpregu.1989.256.3.R757)

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FUKUTA H, MITSUI R, TAKANO H, HASHITANI H: Exercise-induced sympathetic dilatation in arterioles of the guinea pig tibial periosteum. Auton Neurosci 217: 7-17, 2019. https://doi.org/10.1016/j.autneu.2018.12.006

GEROVÁ M: Nitric oxide-compromised hypertension: facts and enigmas. Physiol Res 49: 27-35, 2000.

GEROVÁ M, MASÁNOVÁ C, PAVLÁSEK J: Inhibition of NO synthase in the posterior hypothalamus increases blood pressure in the rat. Physiol Res 44: 131-134, 1995.

GUYTON AC: Dominant role of the kidneys and accessory role of whole-body autoregulation in the pathogenesis of hypertension. Am J Hypertens 2: 575-585, 1989. https://doi.org/10.1093/ajh/2.7.575

KIM SW, LEE J, PÆK YW, KANG DG, CHOI KC: Decreased nitric oxide synthesis in rats with chronic renal failure. J Korean Med Sci 15: 425-430, 2000. https://doi.org/10.3346/jkms.2000.15.4.425

KISHI T: Regulation of the sympathetic nervous system by nitric oxide and oxidative stress in the rostral ventrolateral medulla: 2012 Academic Conference Award from the Japanese Society of Hypertension. Hypertens Res 36: 845-851, 2013. https://doi.org/10.1038/hr.2013.73

KRUM H, SCHLAICH M, WHITBOURN R, SOBOTKA PA, SADOWSKI J, BARTUS K, KAPELAK B, WALTON A, SIEVERT H, THAMBAR Set al.: Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 373: 1275-1281, 2009. https://doi.org/10.1016/S0140-6736(09)60566-3

KVANDOVA M, BARANCIK M, BALIS P, PUZSEROVÁ A, MAJZUNOVA M, DOVINOVA I: The peroxisome proliferator-activated receptor gamma agonist pioglitazone improves nitric oxide availability, renin-angiotensin system and aberrant redox regulation in the kidney of pre-hypertensive rats. J Physiol Pharmacol 69: 231-243, 2018.

LI H, FORSTERMANN U: Uncoupling of endothelial NO synthase in atherosclerosis and vascular disease. Curr Opin Pharmacol 13: 161-167, 2013. https://doi.org/10.1016/j.coph.2013.01.006

LÍŠKOVÁ S, BALIŠ P, MIČUROVÁ A, KLUKNAVSKÝ M, OKULIAROVÁ M, PUZSEROVÁ A, ŠKRÁTEK M, SEKAJ I, MAŇKA J, VALOVIČ P, BERNATOVÁ I: Effect of iron oxide nanoparticles on vascular function and nitric oxide production in acute stress-exposed rats. Physiol Res 69: 1067-1083, 2020. https://doi.org/10.33549/physiolres.934567

LIU J-L, MURAKAMI H, ZUCKER IH: Angiotensin II - nitric oxide interaction on sympathetic outflow in conscious rabbits. Circ Res 82: 496-502, 1998. https://doi.org/10.1161/01.RES.82.4.496

MATSUOKA H, NISHIDA H, NOMURA G, VLIET BNV, TOSHIMA H: Hypertension induced by nitric oxide synthesis inhibition is nerve dependent. Hypertension 23: 971-975, 1994. https://doi.org/10.1161/01.HYP.23.6.971

McBRYDE FD, LIU BH, ROLOFF EV, KASPAROV S, PATON JFR: Hypothalamic paraventricular nucleus neuronal nitric oxide synthase activity is a major determinant of renal sympathetic discharge in conscious Wistar rats. Exp Physiol 103: 419-428, 2018. https://doi.org/10.1113/EP086744

MISCHEL NA, SUBRAMANIAN M, DOMBROWSKI MD, LLEWELLYN-SMITH JJ, MUELLER PJ: (In)activity-related neuroplasticity in brainstem control of sympathetic outflow: unraveling underlying molecular, cellular, and anatomical mechanisms. Am J Physiol Heart Circ Physiol 309: H235-H243, 2015. https://doi.org/10.1152/ajphp.00929.2014

ORESCANIN Z, MILOVANOVIĆ SR: Effect of L-arginine on the relaxation caused by sodium nitroprusside on isolated rat renal artery. Acta Physiol Hung 93: 271-283, 2006. https://doi.org/10.1556/APhysiol.93.2006.4.3

OSBORN JW, AVERINA VA, FINK GD: Current computational models do not reveal the importance of the nervous system in long-term control of arterial pressure. Exp Physiol 94: 389-396, 2009. https://doi.org/10.1113/expphysiol.2008.043281

OSBORN JW, JACOB F, GUZMAN P: A neural set point for the long-term control of arterial pressure: beyond the arterial baroreceptor reflex. Am J Physiol Regul Integr Comp Physiol 288: R846-R855, 2005. https://doi.org/10.1152/ajpregu.00474.2004

PARK S, HARRISON-BERNARD LM: Augmented renal vascular nNOS and renin protein expression in angiotensin type 1 receptor null mice. J Histochem Cytochem 56: 401-414, 2008. https://doi.org/10.1369/jhc.2007.950220
PATEL KP, XU B, LIU X, SHARMA NM, ZHENG H: Renal denervation improves exaggerated sympathoexcitation in rats with heart failure: a role for neuronal nitric oxide synthase in the paraventricular nucleus. Hypertension 68: 175-184, 2016. https://doi.org/10.1161/HYPERTENSIONAHA.115.06794

ROSSI NF, MALISZEWSKA-SCISLO M, CHEN H, BLACK SM, SHARMA S, RAVIKOV R, AUGUSTYNIAK RA: Neuronal nitric oxide synthase within paraventricular nucleus: blood pressure and baroreflex in two-kidney, one-clip hypertensive rats. Exp Physiol 95: 845-857, 2010. https://doi.org/10.1113/expphysiol.2009.051789

THOMSON SC: Nitric oxide mediates anomalous tubuloglomerular feedback in rats fed high-NaCl diet after subtotal nephrectomy. Am J Physiol Renal Physiol 316: F223-F230, 2019. https://doi.org/10.1152/ajprenal.00066.2018

VAVŘÍNOVÁ A, BEHULIAK M, BENCZE M, VODIČKA M, ERGANG P, VANĚČKOVÁ I, ZICHA J: Sympathectomy-induced blood pressure reduction in adult normotensive and hypertensive rats is counteracted by enhanced cardiovascular sensitivity to vasoconstrictors. Hypertens Res 42: 1872-1882, 2019. https://doi.org/10.1038/s41440-019-0319-2

VAZIRI ND, NI Z, OVEISI F: Upregulation of renal and vascular nitric oxide synthase in young spontaneously hypertensive rats. Hypertension 31: 1248-1254, 1998a. https://doi.org/10.1161/01.HYP.31.6.1248

VAZIRI ND, NI Z, WANG XQ, OVEISI F, ZHOU XJ: Downregulation of nitric oxide synthase in chronic renal insufficiency: role of excess PTH. Am J Physiol Renal Physiol 274: F642-F649, 1998b. https://doi.org/10.1152/ajprenal.1998.274.4.F642

ZHANG K, MAYHAN WG, PATEL KP: Nitric oxide within the paraventricular nucleus mediates changes in renal sympathetic nerve activity. Am J Physiol 273: R864-R872, 1997. https://doi.org/10.1152/ajpregu.1997.273.3.R864