# Role of autonomic nervous system in the pathomechanism of hypertension

**Michał Zamojski[1], Zbigniew Dubielski[1], Bartosz Wiechecki[1], Olga Możeńska[1], Jan Gieraltowski[3], Dariusz Artur Kosior[2]**

[1]*Department of Cardiology and Hypertension, Central Research Hospital of the Ministry of the Interior, Warsaw*
[2]*Department of Cardiology and Hypertension, Central Research Hospital of the Ministry of Interior, Warsaw; Mossakowski Institute of Experimental and Clinical Medicine, Polish Academy of Sciences, Warsaw, Poland*
[3]*Faculty of Physics, Warsaw University of Technology, Warsaw*

## Abstract

Due to high prevalence of hypertension (HT) in worldwide population, all aspects of this disease are studied in order to understand its pathogenesis and the influence on human body, as well as in order to find proper treatment. Impaired balance of autonomic nervous system (ANS) is taken into account as one of the main causes elevating blood pressure (BP). It seems that over-activation of sympathetic nervous system (SNS) is the most important factor in pathogenesis of HT. There are some methods which allow us to measure the sympathetic and parasympathetic nervous system activity. Some of them are described below and the influence of impaired ANS balance on HT development is presented. Many different, natural and pathologic factors can cause SNS response, so the measurement of the sole ANS activity cannot fully answer the question about the pathomechanism underlying HT. In this paper, we present some hypotheses regarding possible mechanisms of the disease progression. In primary HT, impairment of baroreceptors response is considered one of such mechanisms. Another one is the influence of hyperinsulinemia on the activation of SNS in insulin resistant patients. A few other factors are considered, like obesity, salt intake, sodium retention and alcohol intake and they are described briefly in our paper. In secondary hypertension, SNS can be activated indirectly by comorbidities, and this pathomechanism is also discussed.

**Key words:** sympathetic nervous system; parasympathetic nervous system; essential hypertension; sympathetic activation; catecholamines

*Arterial Hypertens. 2016, vol. 20, no. 1, pages: 21–25*
*DOI: 10.5603/AH.2016.0005*

## Background

Taking into account very high occurrence of HT in the worldwide population, it is obvious that understanding the pathogenesis of this disease is especially important. Hypertension appears to affect 30–45% of the general European population and this number increases with age [1]. Uncontrolled HT increases the risk of fatal cardiac, cerebral and renal events and leads to target organ damage [2]. From the clinical point of view one can differentiate primary and secondary HT. Essential HT (EHT) is the most common in population and accounts for over 90% of all HT cases [3]. It is described as HT, in which there are no secondary causes of increased BP [4]. The essential hypertension is a highly heterogeneous disease and does not have one assigned pathomechanism, however it is considered a result of coexistence of many pathologic factors [5, 6]. The autonomic nervous system is considered the main factor taking part in the origin of EHT with the specified predominant role of SNS [7].

**Address for correspondence:** Dariusz Artur Kosior, MD, PhD, FESC, FACC
Department of Cardiology and Hypertension, Central Research Hospital of the Ministry of the Interior
Wołoska 137, 02–507 Warsaw
tel.: +48 (22) 508 16 70; fax: +48 (22) 508 16 80
e-mail: Dariusz.Kosior@cskmswia.pl

Activation may be spontaneous, stemming from direct ANS pathology or caused by so called hypertensinogenic factors such as obesity, insulin resistance, high alcohol intake, high salt intake, stress and dyslipidemia [3]. The possible mechanisms of mentioned SNS activation are described below. Secondary HT occurs as a result of other diseases. The most common are: renovascular disease, renal failure, aldosteronism, pheochromocytoma, mendelian forms, obstructive sleep apnea, and drug administration [8].

## Measurement methods

There are papers showing the primary role of the ANS in EHT [9–12]. In early stages of HT, which are characterized by hyperkinetic circulation, reduced activity of parasympathetic nervous system was observed. To investigate this phenomena Julius *et al.* performed a study using the method which is based on intravenous injection of atropine preceded by intravenous injection of propranolol [9]. Atropine is an antagonist of acetylcholine — the vagal nerve neurotransmitter. Atropine combines with muscarinic receptors in the heart and prevents normal impact of acetylcholine on heart function modulation. As a result of intravenous injection of atropine, heart rate and cardiac output increase [9, 13]. This change is smaller in EHT patients than in normotensive patients [9]. Exact data are shown in Table I.

Cardiac index after propranolol and atropine is an average of two readings taken 5 and 7 min after the injection. Heart rate and cardiac index after propranolol and atropine represent readings after 7 min. Cardiac index = liters/min/m2; heart rate = beats/min. Based on [9].

Also administrating small doses of phenylephrine or nitroprusside to stimulate or deactivate baroreceptors might be used to test parasympathetic component in baroreceptor reflex. Effect in essential hypertensive patients was much less reflex bradycardia and tachycardia than in normotensive patients with superimposable results of muscle sympathetic nerve activity [10] (Table II).

Sympathetic nervous system activity can also be measured and it is proven that increased activation of SNS correlates with EHT occurrence [11, 14]. The first method to show this over-activation is measuring plasma catecholamine level. Catecholamines are considered an indirect index of SNS activation and were found to be increased in hypertensive patients [14] (Table III).

The second method is based on measurement of regional norepinephrine overflow to plasma. Esler *et al.* proved that mean norepinephrine spillover is higher in primary hypertensive subjects than in normotensive ones [11]. It also indicated on over-activation of SNS in the hypertensive subjects [11]. Level of SNS activation could also be assessed by microneurography, which measures muscle sympathetic nerve activity. Grassi *et al.* conducted a study using this method.

**Table I.** Mean and standard error of hemodynamic measurements after propranolol administration, and atropine administration in hypertensive and normotensive patients

| | | Patients (N = 11) | Control subjects (N = 16) | P value |
|---|---|---|---|---|
| On propranolol | Cardiac index | 3.23 ± 0.2 | 2.61 ± 0.1 | < 0.01 |
| | Heart rate | 65 ± 2.5 | 57.2 ± 2.3 | < 0.05 |
| On atropine after propranolol | Cardiac index | 3.63 ± 0.22 | 3.45 ± 0.14 | Ns |
| | Heart rate | 98.4 ± 3.6 | 101 ± 3.6 | Ns |
| Change: Propranolol to atropine | Cardiac index | +0.4 ± 0.17 | +0.83 ± 0.2 | < 0.05 |
| | Heart rate | +33.4 ± 3.7 | +43.9 ± 5 | < 0.06 |

**Table II.** Heart rate and muscle sympathetic nerve activity (MSNA) sensitivity changes in 3 groups of patients after intravenous infusion of phenylephrine and nitroprusside

| | | Normotensive Subjects (n = 15) | Moderate EH (n = 14) | Severe EH (n = 14) |
|---|---|---|---|---|
| Phenylephrine | ΔHR/ΔMAP (b × $min^{-1}$/mm Hg) | –1.23 ± 0.2 | –0.82 ± 0.1* | –0.65 ± 0.1* |
| | ΔMSNA/ΔMAP (%i.a./mm Hg) | –6.72 ± 0.5 | –6.48 ± 0.3 | –7.21 ± 0.5 |
| Nitroprusside | ΔHR/ ΔMAP (b × $min^{-1}$/mm Hg) | –2.20 ± 0.1 | –1.55 ± 0.2* | –1.3 ± 0.1* |
| | ΔMSNA/ΔMAP (%i.a./mm Hg) | –13.0 ± 2.1 | –12.5 ± 1.3 | –13.7 ± 1.2 |

HR — heart rate; MAP — mean arterial pressure; MSNA — muscle sympathetic nerve activity; EH — essential hypertension; Mean arterial pressure gradient showed no significant differences between all groups of patients (based on [10]). *P < 0.01

**Table III.** Reference values of plasma and urinary catecholamines levels

| | | | |
|---|---|---|---|
| Adrenaline | Supine (30 min) | P | < 273 pmol/L |
| | Sitting | P | < 328 pmol/L |
| | Standing (30 min) | P | < 4,914 pmol/L |
| | | U | 0–109 nmol/24h |
| Noradrenaline | Supine (30 min) | P | 650–2,423 pmol/L |
| | Sitting | P | 709–4,019 pmol/L |
| | Standing (30 min) | P | 739–4,137 pmol/L |
| | | U | nmol/24h |

*P — plasma, U — urine. Data taken from reference [15]

**Table IV.** Differences in microneurography results between hypertensive and normotensive patients

| | Normotensive Subjects (n = 15) | Moderate EH (n = 14) | Severe EH (n = 14) |
|---|---|---|---|
| MSNA, bursts per min | 27.5 ± 2.5 | 39.2 ± 2.5 * | 48.5 ± 2.4*,** |
| MSNA, bursts per 100 beats | 40.3 ± 3.3 | 55.6 ± 4.12 * | 68.2 ± 4.1*,** |

MSNA — muscle sympathetic nerve activity; EH — essential hypertension (based on [10]). *P < 0.01 vs controls; **P < 0.01 vs moderate EH

They placed a microelectrode in the peroneal nerve. Compared results of hypertensive and normotensive subjects confirmed that increased activation of SNS occurred in EHT. The same study revealed that muscle sympathetic nerve activity was not increased in subjects with secondary HT [10] (Table IV).

## Proposed mechanisms in essential hypertension

All tests described above show that the ANS function is changed in patients with EHT in comparison to normotensive ones [9, 10, 12, 16]. There are a couple of possible mechanisms thought to be responsible for EHT [6, 17–25]. The first possible explanation is the impairment of baroreceptors response. The parasympathetic nervous system is not able to inhibit the increase of BP as it happens in normally functioning baroreflex [17]. As a result, sympathetic tone prevails in modulation. Despite impairment of parasympathetic component, sympathetic tone is preserved. The baroreceptors sensitivity is reseting towards elevated BP and is considered an important component of high BP maintenance [26].

Other proposed mechanism is influence of hyperinsulinemia in insulin resistant patients on activation of SNS [18]. The theory was created after study on animals and humans in which a high dose of insulin was given to subjects and the SNS activation was noticed [27, 28].

Obesity is the next important and common hypertensinogenic factor [29]. Few mechanisms of obese increased sympathetic activity have been suggested, including the role of rennin-angiotensin-aldosterone system from which angiotensin II is considered an active agent causing sympathetic activation and pressor responses, role of impaired baroreceptor sensivity, hyperinsulinemia, increased free faty acids cirrculation and adipokines level [19]. Animal models with high fat and carbohydrate intake developed a significant rise in BP due to enhanced peripheral alpha-1- and beta-adrenergic receptor sensitivity [30]. Corresponding results were reported in human studies. Blood pressure of the obese patients after one month of alpha- and beta-adrenergic receptor pharmacological blockade was reduced noticeably more than BP of the lean ones [31].

Series of studies proved the role of salt intake and sodium retention as HT impact factors, and now it is accepted as common knowledge [20–23]. Over the years, the concept of salt sensitivity has been established as a result of observation of heterogeneous responses to salt intake and divided patients into salt sensitive and salt resistant in both, normal and HT groups [32, 33]. Results from the study showing high salt intake associated with SNS activation are shown in Table V [34].

HouRong *et al.* revealed that plasma norepinephrine concentration, indirect index of SNS activity level, was elevated and significantly higher in salt sensitive patients compared to salt resistant individuals [32].

The high intake of alcohol can also influence ANS activity and there are several possible explanations to this phenomenon. These are: the induction of central nervous system, the reduction of baroreceptor reflexes, SNS activation or discharge of catecholamine or activation of renine-angiotensin-aldosterone system [6, 24, 25].

**Table V.** Influence of daily sodium intake on SNS activation in normal, salt-sensitive and salt-resistant patients

| Daily sodium intake | Subjects | Plasma epinephrine [ng/dl] | Plasma norepinephrine [ng/dl] | Plasma renin activity [ng/ml/hr] |
|---|---|---|---|---|
| 10 mEq | Normal (n = 10) | 4.70 ± 0.75 | 22 ± 3.36 | 5.6 ± 1.17 |
| | Salt-sensitive (n = 12) | 1.6 ± 0.3** | 19.8 ± 1.86 | 3.6 ± 0.64 |
| | Salt-resistant (n = 8) | 2.2 ± 0.65** | 17.2 ± 4.48 | 5.2 ± 1.19 |
| 200 mEq | Normal (n = 10) | 1.95 ± 0.41** | 12 ± 2.22 | 1.5 ± 0.37 |
| | Salt-sensitive (n = 12) | 1.87 ± 0.3 | 21.9 ± 3.19* | 1.32 ± 0.17 |
| | Salt-resistant (n = 8) | 1.61 ± 0.86 | 12.5 ± 2.36 | 1.28 ± 0.28 |

Based on [34]. *P < 0.05; **P < 0.01

## Secondary hypertension and autonomic nervous system

Autonomic nervous system can also be involved in secondary hypertension. As a result of primary disease, ANS is secondarily activated and leads to HT [35–39]. Hypothyroidism is one of such diseases [36–38]. The possible explanation of the association between hypothyroidism and HT might be the influence of thyroid hormones on SNS probably by regulating adrenergic receptor function and density [36, 37, 40]. The number of beta-adrenergic receptors is decreased, therefore, $\alpha$-adrenergic responses increase what possibly leads to the increase in systemic vascular resistance [37].

The next disease worth mentioning is hyperparathyroidism. Parathormone has a direct effect on renin secretion. Activation of the renin-angiotensin-aldosterone axis and enhanced sensitivity to the norepinephrine may contribute to the prevalence of HT and to the vessel sensitization to pressor agents [41]. Also, renin-angiotensin-aldosterone axis is activated in renovascular diseases. Due to chronic ischemia of kidney caused by renal artery stenosis, the secretion of renin is significantly increased which leads to high level of angiotensin in plasma [42, 43]. It is necessary to mention obstructive sleep apnea as an important SNS activating disorder [44]. Although obstructive sleep apnea elevates SNS output due to multiple pathways, hypoxemia is suggested to be the main factor [45–47]. Intermittent hypoxia results in BP elevation that persist even after removal of hypoxemic factor [48]. Possible mechanisms include abnormal baroreceptor reflex function and impaired chemoreflex sensitivity [49–51]. Chen *et al.* suggested the role of endothelin in hypoxemia-induced increase of chemoreceptor activity. Functional studies revealed that endothelin increases stimulus-evoked intracellular Ca2+ levels, thereby potentiates chemoreceptor responses [52]. Continuous hypoxemia increase expression of endothelin A receptor and of preproendothelin in the carotid body, therefore enhance chemoreceptor activity [53]. Another mechanism causing HT could be gene mutations. There are a few described mutations, which induce HT by different pathways. These mutations may influence hormone metabolism and lead to disturbances in renin-angiotensin-aldosterone system. Mutations can affect many other genes important in appropriate modulation of BP but this topic goes beyond this article and mechanism and more examples will not be discussed more accurately [54].

## Conclusions

Understanding the mechanisms of HT, in this case these correlated to ANS, may provide important information about the appropriate prevention, treatment or even the prediction of HT progression itself or other concomitant diseases. Induced SNS activity in HT may lead to left ventricle hypertrophy and hypertrophy and remodeling of arterial walls so the effective treatment is crucial. Discussed papers provide strong evidence for the role of ANS in the pathomechanism of HT. Antihypertensive therapy should concentrate more on having an influence on ANS. Such effect can be obtained by non-pharmacological therapy, antihypertensive drugs or as a result of both. Despite many studies conducted in this area, there are still many mechanisms that need to be revealed to improve our knowledge and to fully explain the pathomechanism of HT.

## References

1. Mancia G., Fagard R., Narkiewicz K. *et al.* 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J. Hypertens. 2013; 31: 1281–1357.
2. Messerli F.H., Williams B., Ritz E. Essential hypertension. Lancet 2007; 370: 591–603.
3. Carretero O.A., Oparil S. Essential hypertension. Part I: definition and etiology. Circulation 2000; 101: 329–335.

4. Raj M., Krishnakumar R. Hypertension in children and adolescents: epidemiology and pathogenesis. Indian J. Pediatr. 2013; 80 (Suppl 1): S71–76.
5. Ehret G.B., Munroe P.B., Rice K.M. *et al.* Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature 2011; 478: 103–109.
6. Grassi G., Seravalle G., Trevano F.Q. *et al.* Neurogenic abnormalities in masked hypertension. Hypertension 2007; 50: 537–542.
7. Grassi G., Seravalle G., Dell'Oro R. *et al.* Adrenergic and reflex abnormalities in obesity-related hypertension. Hypertension 2000; 36: 538–542.
8. Pullalarevu R., Akbar G., Teehan G. Secondary Hypertension, Issues in Diagnosis and Treatment. Prim Care. 2014; 41: 749–764.
9. Julius S., Pascual A.V., London R. Role of parasympathetic inhibition in the hyperkinetic type of borderline hypertension. Circulation 1971; 44: 413–418.
10. Grassi G., Cattaneo B.M., Seravalle G., Lanfranchi A., Mancia G. Baroreflex control of sympathetic nerve activity in essential and secondary hypertension. Hypertension 1998; 31: 68–72.
11. Esler M., Jennings G., Lambert G. Noradrenaline release and the pathophysiology of primary human hypertension. Am. J. Hypertens. 1989; 2: 140S–146S.
12. Solt V.B., Brown M.R., Kennedy B., Kolterman O.G., Ziegler M.G. Elevated insulin, norepinephrine, and neuropeptide Y in hypertension. Am. J. Hypertens. 1990; 3: 823–828.
13. Jones P., Dauger S., Peters M.J. Bradycardia during critical care intubation: mechanisms, significance and atropine. Arch. Dis. Child. 2012; 97: 139–144.
14. Goldstein D.S. Plasma catecholamines and essential hypertension. An analytical review. Hypertension 1983; 5: 86–99.
15. Kratz A., Ferraro M., Sluss P.M., Lewandrowski K.B. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Laboratory reference values. N. Engl. J. Med. 2004; 351: 1548–1563.
16. Esler M., Lambert G., Jennings G. Regional norepinephrine turnover in human hypertension. Clin. Exp. Hypertens. A. 1989; 11 (Suppl. 1): 75–89.
17. Mancia G., Grassi G., Ferrari A.U. Reflex control of the circulation in experimental and human hypertension. In: Zanchetti A., Mancia G., editors. Handbook of Hypertension, Vol 17: Pathophysiology of Hypertension. Elsevier Science, Amsterdam 1997: 568–601.
18. Grassi G. Adrenergic overdrive as the link among hypertension, obesity, and impaired thermogenesis: lights and shadows. Hypertension 2007; 49: 5–6.
19. Fukiyama K., McCubbin J.W., Page I.H. Chronic hypertension elicited by infusion of angiotensin into vertebral arteries of unanaesthetized dogs. Clin. Sci. 1971; 40: 283–291.
20. Ha SK. Dietary salt intake and hypertension. Electrolyte Blood Press 2014; 12: 7–18.
21. Bock A. The influence of salt intake on hypertension. Ther. Umsch. 2009; 66: 721–724.
22. Lurbe E., Redon J., Kesani A. *et al.* Increase in nocturnal blood pressure and progression to microalbuminuria in type 1 diabetes. N. Engl. J. Med. 2002; 347: 797–805.
23. Dustan H.P., Valdes G., Bravo E.L., Tarazi R.C. Excessive sodium retention as a characteristic of salt-sensitive hypertension. Am. J. Med. Sci. 1986; 292: 67–74.
24. Howes L.G., Reid J.L. The effects of alcohol on local, neural and humoral cardiovascular regulation. Clin. Sci. (Lond.) 1986; 71: 9–15.
25. Rupp H., Brilla C.G., Maisch B. Hypertension and alcohol: central and peripheral mechanisms. Herz 1996; 21: 258–264.
26. Grassi G. Role of the sympathetic nervous system in human hypertension. J. Hypertens. 1998; 16: 1979–1987.
27. Scherrer U., Sartori C. Insulin as a vascular and sympathoexcitatory hormone: implications for blood pressure regulation, insulin sensitivity, and cardiovascular morbidity. Circulation 1997; 96: 4104–4113.
28. Anderson E.A., Balon T.W., Hoffman R.P., Sinkey C.A., Mark A.L. Insulin increases sympathetic activity but not blood pressure in borderline hypertensive humans. Hypertension 1992; 19: 621–627.
29. Hossain P., Kawar B., El Nahas M. Obesity and diabetes in the developing world — a growing challenge. N. Engl. J. Med. 2007; 356: 213–215.
30. Rocchini A.P., Yang J.Q., Gokee A. Hypertension and insulin resistance are not directly related in obese dogs. Hypertension 2004; 43: 1011–1016.
31. Wofford M.R., Hall J.E. Pathophysiology and treatment of obesity hypertension. Curr. Pharm. Des. 2004; 10: 3621–3637.
32. Hou R., Liu Z., Liu J. *et al.* The circadian rhythm of blood pressure and the effect of salt intake in salt-sensitive subjects. Chin. Med. J. (Engl). 2000; 113: 22–26.
33. Sullivan J.M. Salt sensitivity. Definition, conception, methodology, and long-term issues. Hypertension 1991; 17 (1 Suppl.): I61–68.
34. Campese V.M., Romoff M.S., Levitan D. *et al.* Abnormal relationship between sodium intake and sympathetic nervous system activity in salt-sensitive patients with essential hypertension. Kidney Int. 1982; 21: 371–378.
35. Spallone V., Gambardella S., Maiello M.R. *et al.* Relationship between autonomic neuropathy, 24-h blood pressure profile, and nephropathy in normotensive IDDM patients. Diabetes Care 1994; 17: 578–584.
36. Ripoli A., Pingitore A., Favilli B. *et al.* Does subclinical hypothyroidism affect cardiac pump performance? Evidence from a magnetic resonance imaging study. J. Am. Coll. Cardiol. 2005; 45: 439–.45.
37. Richelsen B., Sørensen N.S. Alpha 2- and beta-adrenergic receptor binding and action in gluteal adipocytes from patients with hypothyroidism and hyperthyroidism. Metabolism 1987; 36: 1031–1039.
38. Mancia G., Sega R., Bravi C. *et al.* Ambulatory blood pressure normality: results from the PAMELA study. J. Hypertens. 1995; 13: 1377–1390.
39. Pedrosa R.P., Drager L.F., Gonzaga C.C. *et al.* Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension 2011; 58: 811–817.
40. Williams R.S., Lefkowitz R.J. The effect of thyroid hormone on adrenergic receptors. In: Oppenheimer J.H. (ed.). Molecular Basis of Thyroid Hormone Action. Academic Press, London 1983: 325–349.
41. Gennari C., Nami R., Gonnelli S. Hypertension and primary hyperparathyroidism: the role of adrenergic and renin-angiotensin-aldosterone systems. Miner Electrolyte Metab. 1995; 21: 77–81.
42. Welch W.J. The pathophysiology of renin release in renovascular hypertension. Semin. Nephrol. 2000; 20: 394–401.
43. Ram C.V., Clagett G.P., Radford L.R. Renovascular hypertension. Semin. Nephrol. 1995; 15: 152–174.
44. Somers V.K., Dyken M.E., Clary M.P., Abboud F.M. Sympathetic neural mechanisms in obstructive sleep apnea. J. Clin. Invest. 1995; 96: 1897–1904.
45. Seif F., Patel S.R., Walia H.K. *et al.* Obstructive sleep apnea and diurnal nondipping hemodynamic indices in patients at increased cardiovascular risk. J. Hypertens. 2014; 32: 267–275.
46. Kario K., Schwartz J.E., Pickering T.G. Ambulatory physical activity as a determinant of diurnal blood pressure variation. Hypertension 1999; 34: 685–691.
47. Fava C., Montagnana M., Favaloro E.J., Guidi G.C., Lippi G. Obstructive sleep apnea syndrome and cardiovascular diseases. Semin. Thromb. Hemost. 2011; 37: 280–297.
48. Fletcher E.C., Miller J., Schaaf J.W., Fletcher J.G. Urinary catecholamines before and after tracheostomy in patients with obstructive sleep apnea and hypertension. Sleep 1987; 10: 35–44.
49. Parati G., Di Rienzo M., Bonsignore M.R. *et al.* Autonomic cardiac regulation in obstructive sleep apnea syndrome: evidence from spontaneous baroreflex analysis during sleep. J. Hypertens. 1997; 15: 1621–1626.
50. Swislocki A.L., Hoffman B.B., Reaven G.M. Insulin resistance, glucose intolerance and hyperinsulinemia in patients with hypertension. Am. J. Hypertens. 1989; 2: 419–423.
51. Narkiewicz K., Pesek C.A., Kato M. *et al.* Baroreflex control of sympathetic nerve activity and heart rate in obstructive sleep apnea. Hypertension 1998; 32: 1039–1043.
52. Chen J., He L., Dinger B., Fidone S. Cellular mechanisms involved in rabbit carotid body excitation elicited by endothelin peptides. Respir. Physiol. 2000; 121: 13–23.
53. Chen J., He L., Dinger B., Stensaas L., Fidone S. Role of endothelin and endothelin A-type receptor in adaptation of the carotid body to chronic hypoxia. Am. J. Physiol. Lung Cell Mol. Physiol. 2002; 282: L1314–1323.
54. Gong M., Hubner N. Molecular genetics of human hypertension. Clin. Sci. (Lond.) 2006; 110: 315–326.