Original review article

Arterial hypertension and significant DNA damage – from cell lines to patients

Radka Hazuková[a,b]

[a] *Department of Internal Medicine I – Cardiology, University Hospital Olomouc, Olomouc, Faculty of Medicine, Palacký University in Olomouc and University Hospital Olomouc, Olomouc, the Czech Republic*
[b] *Department of Cardiology and Internal Medicine (Profi-Kardio, s.r.o.), Horice v Podkrkonosi, the Czech Republic*

ARTICLE INFO

Article history:
Submitted: 9. 8. 2024
Revised: 9. 9. 2024
Accepted: 30. 9. 2024
Available online: 2. 10. 2024

Klíčová slova:
Poškození DNA a zlomy
Doporučené postupy
Hypertenze
Mezery v důkazech
Oprava poškození DNA
Oxidační stres
PARP
Terapeutický cíl

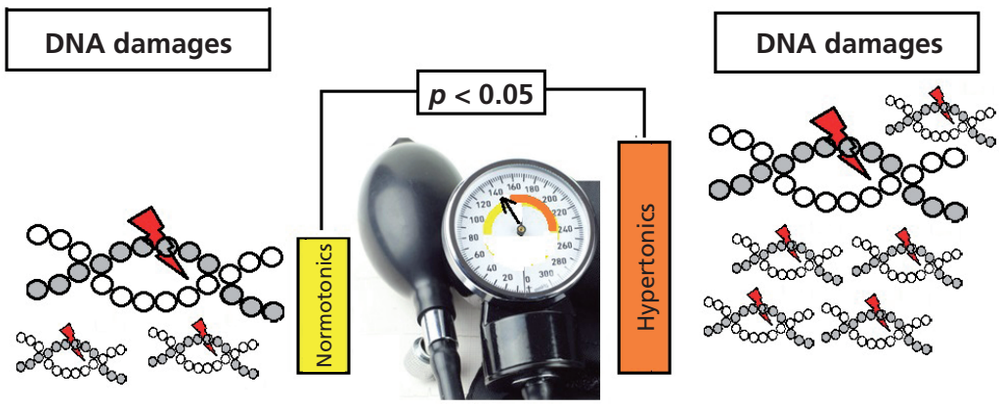
SOUHRN

Arteriální hypertenze (HT) je klíčový rizikový faktor a velmi rozšířené chronické onemocnění, které participuje na rozvoji řady kardiálních a nekardiálních chorob. Proto je HT jednou z důležitých příčin morbidity, invalidity a mortality. Etiologie HT je multifaktoriální. Oxidační stres se zdá být v etiologii HT a ostatních kardiovaskulárních onemocnění (KVO) hlavní hnací silou. Nově je v otázce oxidačního stresu a v genezi KVO diskutována role poškození DNA s výhledem na nové terapeutické cíle. Ve světle současných doporučených postupů s definovanou mezerou v důkazech je cílem tohoto sdělení předložit ucelenou formu studií, které se zabývají významným poškozením DNA u HT – od buněčných kultur k reálným pacientům.

Keywords:
DNA damage and breaks
DNA damage repair
Gaps in the evidence
Guidelines
Hypertension
Oxidative stress
PARP
Therapeutic target

ABSTRACT

Arterial hypertension (HT) is a key risk factor and a widespread chronic disease that contributes to the development of a number of cardiac and non-cardiac diseases. Therefore, HT is one of the important causes of morbidity, disability, and mortality. The aetiology of HT is multifactorial. Oxidative stress appears to be the main driver in the aetiology of HT and other cardiovascular diseases (CVD). The role of DNA damage is newly discussed in the context of oxidative stress and in the genesis of CVD with a view to new therapeutic targets. Regarding current guidelines with defined gaps in the evidence, the aim of this paper was to present a comprehensive form of studies on significant types of DNA damage in HT – from cell cultures to real patients.



Address: MUDr. Radka Hazuková, Ph.D., Department of Cardiology and Internal Medicine (Profi-Kardio, s.r.o.), Klicperova 6, 508 01 Horice v Podkrkonosi, the Czech Republic, e-mail: radka.hazukova@seznam.cz

DOI: 10.33678/cor.2024.075

Please cite this article as: Hazuková R. Arterial hypertension and significant DNA damage – from cell lines to patients. Cor Vasa 2024;66:506–511.

Introduction

Systemic hypertension (HT) is the most important modifiable cardiovascular (CV) risk factor.[1,2] Simultaneously, HT represents a widespread chronic disease affecting 30% of adults.[1,2] About 90% of HT patients have essential/primary HT, where the exact cause remains unknown.[1] HT mediates through metabolic, functional and structural changes cardiac and non-cardiac organ damages and further diseases based on atherosclerotic or non-atherosclerotic lesions.[2] Therefore, HT is one of the main causes of morbidity, disability and mortality.[1,2] Early detection, targeted lifestyle modifications, and adherence to antihypertensive pharmacotherapy can prevent organ complications and repair damaged organs by reverse remodelling principles.[1,2]

The aetiology of HT is multifactorial with complex interactions.[1,2] Exogenous (smoking) and endogenous factors (dyslipidaemia, hyperglycaemia, genetic polymorphisms, epigenetic and posttranslational modifications of antioxidant substances) cause a deviation of the physiological homeostasis of redox reactions in the body with an increase in oxidants (reactive oxygen species [ROS],….).[1,2] This imbalance between oxidants and antioxidants is known as oxidative stress.[3] Oxidative stress with its complex consequences (profibrotic, pro-inflammatory, proliferative) seems to be the basic driving force in the aetiology of vasculopathy, hypertension, and other cardiovascular diseases (CVD). This vasculopathy is characterised with endothelial dysfunction, remodelling of the vascular wall (stiffness, hypertrophy, fibrosis, inflammation, greater intima media thickness, atherosclerosis) and geometric rearrangement of vascular networks.[1,3] Thanks to research advantages on subcellular levels, the role of DNA damage is newly discussed in the context of oxidative stress and in the genesis of CVD.[4–6] DNA damage repair (DDR) substances (e.g. poly-ADP ribose polymerase [PARP]) represent a promising therapeutic target in the innovation of causal pharmacotherapy of HT and other CVD.[4–6]

In the light of the current guidelines, the aim of this paper was to try at least partially to reduce defined gaps in the evidence regarding the HT drivers.[1] Thus this paper provides a systematic schedule of existing results on significant forms of DNA damage in various models of HT (from cell lines to real human patients). The main attention was focused on strictly experimental laboratory conditions to eliminate potential confounders. The purpose was to confirm or refute relatively consistent results from human studies (the elevation of DNA damage in HT), where the interpretation may be altered by complexity of the real human organism with many potential confounders.[7]

Methods

The methods, including the electronic scientific databases, the study period, keywords, inclusion and exclusion criteria, study selection diagram, were described earlier.[7] The novelty and the aim of this work is to summarise studies performed under strictly experimental laboratory conditions (cell and animal models). The results are intended to support the data obtained by analogous research of human studies that were presented earlier.[7] With the effort to present a comprehensive summary of studies from cell cultures to real human patients, we also present a very reduced list of relevant human studies with references to the previous source.[7]

The work is intended for clinicians. For this reason, and due to the absence of relevant data, correlation and meta-analysis have now been omitted from the methods. Only relevant, controlled, prospective studies conducted in accordance with ethical principles were included in the study. The study is based on the significant damage of nuclear (not mitochondrial) DNA. In the order from milder forms to the most severe forms of DNA damages, these are 1) oxidized DNA base (8-hydroxy-2´-deoxyguanosine [8OHdG]), 2) single-strand breaks (SSBs), detectable by comet assay in alkaline conditions, 3) double strand breaks (DSBs), represented by phosphorylated histone gammaH2AX (γH2AX).[7]

A number of studies and other parameters are marked using "N". Data are expressed as mean ± standard deviation (SD) or median (minimum; maximum). Statistically significant differences are defined by the p-value ($p < 0.05$).

Results

Studies

The total number of studies were found (N = 79526), the followings matched the inclusion and the exclusion criteria (N = 33): cell cultures (N = 3 studies) (**Table 1**),[8–10] animal models (N = 15 studies) (**Table 2**),[11–23] human studies (N = 15) (**Table 3**).[7] Human studies have been analysed and presented in details previously, so they are listed here only in basic outlines with the appropriate references (**Table 3**).[7]

Probands

In the context of cell cultures, the number of cells represents the irrelevant information (Table 1). In the animal models, there were enrolled (N = 140), respectively (N = 86), HT individuals after subtracting possible duplicates (N = 54).[13–15,17,19,22,23] The approximate mean and median age of animal HT individuals was 18.5 ± 15.2; 16 (6–72), respectively 22.3 ± 19.0; 16.5 (8–72) weeks after subtracting of possible duplicates. The number of animal normotensive controls was (N = 126), respectively (N = 74), after subtracting possible duplicates (N = 52)[13–15,17,19,22,23] (**Table 2**). In human studies, there were (N = 843) HT adult patients, when subjects with "white coat hypertension" were subtracted (**Table 3**).[7] The average age was of 57.8 ± 6.9 years. In human studies, there were (N=587) normotensive adult controls (**Table 3**).[7]

Elevated DNA damages in HT

In all of the enrolled studies, with the exception of 2 studies (Toljic M, 2017 and Kotani K, 2014)[7] (**Table 3**), the higher level of DNA damage was demonstrated in HT subjects, when comparing with the normotensive controls ($p < 0.05$) (**Tables 1–3**).[7–23]

Table 1 – Oxidative DNA damage – hypertonic cell models

Authors, year[Ref.]	Hypertonic cells (HT)	Healthy cell controls (C)	DNA damage type/method source, units	Comparison using DNA damage level, $p < 0.05$
			8OHdG/IF	
Schmid U, 2008[8]	Yes	Yes	Cells, DNA in tail (%)	C < HT
			SSBs/COMET ASSAY	
Schmid U, 2008[8]	Yes	Yes	Cells, DNA in tail (%)	C < HT
Queisser N, 2011[9]	Yes	Yes	Cells, DNA in tail (%)	C < HT
			DSBsγ/H2AX/flow cytometry	
Schmid U, 2008[8]	Yes	Yes	Cells, fold	C < HT
Balhorn R, 2020[10]	Yes	Yes	Cells, normalized ratio	C < HT

8OHdG – 8-hydroxyl-2´-deoxyguanosine; γH2AX – gammaH2AX, phosphorylated histone H2AX; DNA – deoxyribonucleic acid; DSBs – double strand breaks; HT – arterial hypertension; IF – immunofluorescence; Ref. – reference; SSBs – single strand breaks.
Statistically significant when *p*-value < 0.05.

Table 2 – Oxidative DNA damage – hypertonic animals

Authors, year[Ref.]	Hypertonics (HT) *N (age; weeks)*	Healthy controls (C) *N (matched)*	DNA damage type/method *source, units*	Comparison using DNA damage level, $p < 0.05$
			8OHdG/ELISA	
Negishi H, 1999[11]	15 (14–18)	9	Urine, $ng.kg^{-1}$ per day	C < HT
Negishi H, 2000[12]	5 (14)	5	Urine, $ng.mg^{-1}.creatinine^{-1}$	C < HT
Queisser N, 2013[13]	8 (8)	5	Kidney, positive cells (%)	C < HT
			8OHdG/MS	
Schupp N, 2011[14]	7 (8)	6	Kidney, LC-MS/MS, 106 dG	C < HT
Brand S, 2013[15]	6 (17)	7	Urine, $ng.20h^{-1}$	C < HT
			SSBs/COMET ASSAY	
Schupp N, 2011[14]	7 (8)	6	Kidney, DNA in tail (%)	C < HT
Queisser N, 2013[13]	8 (13)	5	Kidney, mean tail DNA (%)	C < HT
Dias AT, 2014[16]	10 (14)	8	Kidney, DNA in tail (%), tail moment (A.U.)	C < HT
Zimnol A, 2017[17]	6 (19)	8	Kidney, DNA in tail (%)	C < HT
Saheera S, 2017[18]	3 (48–72)	3	Heart, tail moment	C < HT
Zimnol A, 2020[19]	6 (18–22)	5	Kidney, DNA in tail (%)	C < HT
Bruic M, 2021[20]	8 (24)	8	Blood, liver, heart, kidney, A.U.	C < HT
			DSBs/γH2AX/FLOW CYTOMETRY	
Baban B, 2013[20,21]	5 (NA)	4	Heart, positive cells	C < HT
			DSBs/γH2AX/IF/IHCH	
Schupp N, 2011[14]	7 (8)	6	Kidney, positive cells (%)	C < HT
Brand S, 2013[15]	6 (17)	8	Heart, kidney, positive cells	C < HT
Queisser N, 2013[13]	8 (13)	5	Kidney, positive cells (%)	C < HT
Brand S, 2014[22]	6 (17)	7	Heart, kidney, positive $nuclei.mm^{-2}$	C < HT
Queisser N, 2014[23]	8 (6–7)	8	Liver, positive nuclei (%)	C < HT
Zimnol A, 2017[17]	6 (19)	8	Kidney, positive cells	C < HT
Zimnol A, 2020[19]	5 (18–22)	5	Kidney, positive cells	C < HT

8OHdG – 8-hydroxyl-2´-deoxyguanosine; γH2AX – gammaH2AX, phosphorylated histone H2AX; A.U. – arbitrary unit; DNA – deoxyribonucleic acid; DSBs – double strand breaks; ELISA – enzyme-linked immuno sorbent assay; HT – arterial hypertension; IF – immunofluorescence; IHCH – imunohistochemically; LC-MS/MS – liquid chromatography–mass spectrometry-mass spectrometry; Ly – lymphocytes; mean tail DNA – percentage of fluorescence intensity in the tail region; MS – mass spectrometry; PBC – peripheral blood cell; Ref. – reference; SSBs – single strand breaks. Statistically significant when *p*-value < 0.05.

Table 3 – Oxidative DNA damage – hypertonic humans[7]

Authors, year	Hypertonics (HT) *N (age; years)*	Healthy controls (C) *N (matched)*	DNA damage type/method *source, units*	Comparison using DNA damage level, $p < 0.05$
			8OHdG/ELISA	
Lee J, 2005	38 (54.0 ± 12.0)	22	Plasma, ng.ml^{-1}	C < HT
Toljic M, 2017	21 (32.0; 23.0–38.0)	28	Plasma, nM	C = HT
Zhao Y, 2020	63 (72.1 ± 7.9)	84	Serum, ng.ml^{-1}	C < HT
Negishi H, 2000	38 (52.0 ± 0.5)	22	Urine, ng.mg^{-1} creatinine^{-1}	C < HT
Negishi H, 2001	8 (52.0 ± 0.7)	22	Urine, ng.mg^{-1} creatinine^{-1}	C < HT
Subash P, 2010	105 (45.0 ± 9.0)	75	Urine, ng.mg^{-1} creatinine^{-1}	C < HT
Kotani K, 2014	45 (62.0 ± 9.0)	31	Urine, ng.mg^{-1} creatinine^{-1}	C = HT
Yavuzer S, 2016	30 (72.6 ± 8.7)	30	Urine, ng.mg^{-1} creatinine^{-1}	C < HT
Yavuzer S, 2016	30 (43.6 ± 3.9)	30	Urine, ng.mg^{-1} creatinine^{-1}	C < HT
Yıldırım E, 2017	40 (44.4 ± 3.9)	40	Urine, ng.mg^{-1} creatinine^{-1}	C < HT
			SSBs/COMET ASSAY	
Gur M, 2007	84 (50.0 ± 6.0)	24	PBCs/Ly/, A.U.	C < HT
Yildiz A, 2008	21 (45.0 ± 7.0)	19	PBCs/Ly/, A.U.	C < HT
Subash P, 2010	80 (50.0 ± 9.0)	50	PBCs/Ly/, A.U.	C < HT
Gür M, 2013	64 (47.9±7.0)	20	PBCs/Ly/, A.U.	C < HT
Saiedullah M, 2013	46 (41.0±5.0)	40	PBCs/Ly/, A.U.	C < HT
Subash P, 2016	100 (45.0 ± 12.0)	50	PBCs/Ly/, A.U.	C < HT
			DSBs/γH2AX	
NA	NA	NA	NA	NA

8OHdG – 8-hydroxyl-2´-deoxyguanosine; γH2AX – gammaH2AX, phosphorylated histone H2AX; A.U. – arbitrary unit; DNA – deoxyribonucleic acid; DSBs – double strand breaks; ELISA – enzyme-linked immuno sorbent assay; HT – arterial hypertension; Ly – lymphocytes; NA – not available; PBC – peripheral blood cell; ref. – reference; SSBs – single strand breaks; data are expressed as mean ± standard deviation (mean ± SD). Statistically significant when *p*-value < 0.05.

DNA damage types

With the exception of human studies, which tested only 8OHdG and SSBs (**Table 3**),[7] the other studies (cell and animal models) evaluated all three types of DNA damage (8OHdG, SSBs, DSBs) (**Tables 1, 2**).[8–23]

HT types

In cell cultures, the HT model was induced humorally using angiotensin II (Ang II)[8] or aldosterone (Ald)[9,10] (**Table 1**). In animal studies, various types of HT models were used. Genetically determined (spontaneously hypertensive rats [SHRs]),[12,13,19,21] humorally induced (Ang II,[15,17,19,22] Ald,[13,23] deoxycorticosterone acetate [DOCA][14]), using volume overload-induction,[22] surgically induced (2-kidney 1-clip [2K1C], or aortic banding)[16] and using diet-induction (natrium chloride [NaCl])[13] (**Table 2**). In human studies, two types of HT were assessed – essential and gestational (**Table 3**).[7]

DNA damage – biological materials (source)

A) Cells. DNA damage was evaluated in cell cultures (**Table 1**), but also in animal models (8OHdG, kidneys), (DNA breaks [SSBs and DSBs] in kidneys, heart, and liver) (**Table 2**). Human studies have evaluated only SSBs in peripheral blood cells (lymphocytes) (**Table 3**).[7]

B) Body fluids. In animals, only Bruic 2021 (**Table 2**) evaluated SSBs in blood, others evaluated 8OHdG in urine (**Table 2**). Human studies evaluated 8OHdG in plasma, serum and urine (**Table 3**).[7]

Discussion

Main findings

To the best of our knowledge, this review for the first time summarized studies performed under strictly experimental laboratory conditions (cell and animal models). Summarized experimental data free from confounders consistently confirmed results known from previous review on human studies that DNA damages are elevated in HT when comparing controls.[7] With the aim to create the complete schedule of existing results on significant forms of DNA damages in HT from cell cultures to real patients according to clear selection criteria,[7] relevant human studies are briefly reminded in this paper too. Authors believe based on this paper with experimental results that questions in the interpretation are resolved.

Practical view

From a practical point of view, the most important results are those, which are easily feasible, accessible, reproducible and ethical. Such requirements are met by analysis of DSBs in peripheral blood lymphocytes.

From our point of view, circulating nuclear cells taken from peripheral venous blood (lymphocytes), which reflect the current "steady state" of the whole organism, appear to be the optimal biological material for testing DNA breaks in HT. For practical reasons, we also consider the detection of the most severe forms of DNA damage (DSBs) which is optimal against less serious forms (8OHdG, SSBs).

Unfortunately, this combination (DSBs in peripheral lymphocytes) does not appear in the included HT studies either in humans or in animals.

From the available results, we consider the most important finding available from human studies to be the detection of elevation of SSBs in peripheral blood lymphocytes (N = 395 HT individuals; N = 203 normotensive controls). A similar value represents Bruice 2021 study with animals.[20]

Suitability of biological materials and DNA damage biomarkers

From selected types of DNA damages, the 8OHdG represents the least severe, less specific and more common type. Therefore, from our point of view, 8OHdG is a less suitable biomarker for the clinical practice. DNA damage analysis in urine can be burdened by the unattractive urine collection. The analysis of damaged DNA directly from blood, serum, urine represents the extracellular space analysis, which is of no value for therapeutic consequences, because the cell has already died and irreversibly disintegrated with DNA leakage into the extracellular space. Analysis of damaged DNA from cell tissues (heart, liver, kidneys) seems to be clinically less suitable in the context of HT, because it requires a greater invasive intervention. Therefore, the peripheral blood cell sampling seems to be the best.

The exception from studies

In the presented studies, only two studies demonstrated no significant DNA damage difference between HT individuals and controls. Both were human studies (Toljic, 2017 and Kotani, 2014).[7] There may be several reasons. In both cases, there was treated HT, not untreated. The explanation could lie in the achieving of the optimal blood pressure control in HT individuals. Another explanation could lie in the size of the cohort. In the case of Toljic, it was a relatively small cohort (21 HT individuals), which might not be sufficient to detect a statistically significant 8OHdG difference.[7] On the other hand, in a similarly small cohort (N = 21 HT individuals), Yildiz 2008 recorded a significant increase in SSBs in HT patients.[7] However, Yildiz's cohort consisted of untreated HT subjects.[7]

Another explanation, at least in the case of Toljic, may lie in a gender.[7] Toljic included only premenopausal women and evaluated gestational HT.[7] From the available data, we know that women of childbearing age are relatively protected against oxidative stress, which creates sexual dimorphism. Furthermore, clinical and preclinical data have shown higher values of oxidative stress biomarkers (O_2, H_2O_2) in men/males than in women/females.[24–26] In animal studies, it has been shown that males respond to antioxidants (tempol, apocynin) by lowering blood pressure, females do not.[24–26] This sexual dimorphism is probably due to increased activation of pro-oxidative Nox systems in males and increased antioxidant capacity in females.[27,28]

It has been shown that estradiol reduces the expression and activity of Nox and increases the expression of antioxidant enzymes (superoxide dismutase [SOD] and glutathione peroxidase).[29] In premenopausal females, oxidative stress is blunted by increased activation of antioxidant systems and down-regulation of prooxidant systems.[27–29]

The explanation related to Kotani 2014 study may lie in the coincidence of diabetes mellitus (DM) in both the tested subjects and the control group.[7]

The important finding is that increased level of DNA damage was evidenced in all models of heterogeneously induced HT – with the exception of both the gestational HT and HT in diabetics when comparing normotensive diabetic controls.[7–24]

The presented findings bring a new perspective on the issue of oxidative stress and the genesis of HT and CVD. DNA damages represent a deeper subcellular level when comparing the standard concept of oxidative stress on cellular level with inflammatory, proliferative, and profibrotic cells and substances.

Conclusion

This paper on studies conducted under strictly laboratory experimental conditions for the first time confirmed findings from the complex human organism.[7] HT is associated with increased levels of DNA damage.[7] The results are completely consistent.[7] These findings may be the innovation in the understanding of the HT genesis as well as other CV disease genesis. This paper may partially reduce the gaps in the evidence.[1] The findings may support the innovation in the causal CV disease pharmacotherapy targeted on DDR substances (e.g. PARP).[4–6]

Conflict of interest
None declared.

Funding
Ministry of Health, Czech Republic – Conceptual Development of Research Organization (FNOl, 00098892).

Ethical statement
The work was conducted in accordance with the Declaration of Helsinki.

References

1. McEvoy JW, McCarthy CP, Bruno RM, et al.; ESC Scientific Document Group. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension: Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC)

and endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO). Eur Heart J 2024;ehae178, https://doi.org/10.1093/eurheartj/ehae178
2. Williams B, Mancia G, Spiering W, et al.; Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J 2018;39:3021–3104.
3. Touyz RM, Rios FJ, Alves-Lopes R, et al. Oxidative Stress: A Unifying Paradigm in Hypertension. Can J Cardiol 2020;36:659–670.
4. Hazuková R. Poškození DNA – nová výzva v kardiologii. In: Táborský M, Kautzner J, Linhart A, eds. Kardiologie. X. Kardiovaskulární onemocnění v definovaných populacích. Česká kardiologická společnost, Slovenská kardiologická společnost, 2024:157–168.
5. Hazuková R, Řezáčová M, Kočí J, et al. Severe deoxyribonucleic acid damage after out-of-hospital cardiac arrest in successfully resuscitated humans. Int J Cardiol 2016;207:33–35.
6. Hazuková R, Rezácová M, Köhlerová R, et al. Comet assay in evaluating deoxyribonucleic acid damage after out-of-hospital cardiac arrest. Anatol J Cardiol 2017;18:31–38.
7. Hazukova R, Rezacova M, Pleskot M, et al. DNA damage and arterial hypertension. A systematic review and meta-analysis. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 2024;168:15–24.
8. Schmid U, Stopper H, Schweda F, et al. Angiotensin II induces DNA damage in the kidney. Cancer Res 2008;68:9239–9246.
9. Queisser N, Oteiza PI, Stopper H, et al. Aldosterone induces oxidative stress, oxidative DNA damage and NF-κB-activation in kidney tubule cells. Mol Carcinog 2011;50:123–135.
10. Balhorn R, Hartmann C, Schupp N. Aldosterone Induces DNA Damage and Activation of Nrf2 Mainly in Tubuli of Mouse Kidneys. Int J Mol Sci 2020;21:4679.
11. Negishi H, Ikeda K, Sagara M, et al. Increased oxidative DNA damage in stroke-prone spontaneously hypertensive rats. Clin Exp Pharmacol Physiol 1999;26:482–484.
12. Negishi H, Njelekela M, Ikeda K, et al. Assessment of in vivo oxidative stress in hypertensive rats and hypertensive subjects in Tanzania, Africa. .Hypertens Res 2000;23:285–289.
13. Queisser N, Amann K, Hey V, et al. Blood pressure has only minor influence on aldosterone-induced oxidative stress and DNA damage in vivo. Free Radic Biol Med 2013;54:17–25.
14. Schupp N, Kolkhof P, Queisser N, et al. Mineralocorticoid receptor-mediated DNA damage in kidneys of DOCA-salt hypertensive rats. FASEB J 2011;25:968–978.
15. Brand S, Amann K, Schupp N. Angiotensin II-induced hypertension dose-dependently leads to oxidative stress and DNA damage in mouse kidneys and hearts. J Hypertens 2013;31:333–344.
16. Dias AT, Rodrigues BP, Porto ML, et al. Sildenafil ameliorates oxidative stress and DNA damage in the stenotic kidneys in mice with renovascular hypertension. J Transl Med 2014;12:35.
17. Zimnol A, Amann K, Mandel P, et al. Angiotensin II type 1a receptor-deficient mice develop angiotensin II-induced oxidative stress and DNA damage without blood pressure increase Am J Physiol Renal Physiol 2017;313:F1264–F1273.
18. Saheera S, Nair RR. Accelerated decline in cardiac stem cell efficiency in Spontaneously hypertensive rat compared to normotensive Wistar rat. PLoS One 2017;12:e0189129.
19. Zimnol A, Spicker N, Balhorn R, et al. The NADPH Oxidase Isoform 1 Contributes to Angiotensin II-Mediated DNA Damage in the Kidney. Antioxidants (Basel) 2020;9:586.
20. Bruic M, Grujic-Milanovic J, Miloradovic Z, et al. DNA, protein and lipid oxidative damage in tissues of spontaneously hypertensive versus normotensive rats. Int J Biochem Cell Biol 2021;141:106088.
21. Baban B, Liu JY, Mozaffari MS. Pressure overload regulates expression of cytokines, γH2AX, and growth arrest- and DNA-damage inducible protein 153 via glycogen synthase kinase-3β in ischemic-reperfused hearts. Hypertension 2013;61:95–104.
22. Brand S, Amann K, Mandel P, et al. Oxidative DNA damage in kidneys and heart of hypertensive mice is prevented by blocking angiotensin II and aldosterone receptors. PLoS One 2014 Dec 31;9:e115715.
23. Queisser N, Happ K, Link S, et al. Aldosterone induces fibrosis, oxidative stress and DNA damage in livers of male rats independent of blood pressure ganges. Toxicol Appl Pharmacol 2014;280:399–407.
24. Reckelhoff JF, Romero DG, Yanes Cardozo LL. Sex, Oxidative Stress, and Hypertension: Insights From Animal Models. Physiology (Bethesda) 2019;34:178–188.
25. Ide T, Tsutsui H, Ohashi N, et al. Greater oxidative stress in healthy young men compared with premenopausal women. Arterioscler Thromb Vasc Biol 2002;22:438–442.
26. Bhatia K, Elmarakby AA, El-Remessy AB, et al. Oxidative stress contributes to sex differences in angiotensin II-mediated hypertension in spontaneously hypertensive rats. Am J Physiol Regul Integr Comp Physiol 2012;302:R274–R282. Erratum in: Am J Physiol Regul Integr Comp Physiol 2012;302:R1233.
27. Ji H, Zheng W, Menini S, et al. Female protection in progressive renal disease is associated with estradiol attenuation of superoxide production. Gend Med 2007;4:56–71.
28. Miller AA, Drummond GR, Mast AE, et al. Effect of gender on NADPH-oxidase activity, expression, and function in the cerebral circulation: role of estrogen. Stroke 2007;38:2142–2149.
29. Borrás C, Gambini J, Gómez-Cabrera MC, et al. 17beta-oestradiol up-regulates longevity-related, antioxidant enzyme expression via the ERK1 and ERK2[MAPK]/NFkappaB cascade. Aging Cell 2005;4:113–118.