Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: April 30, 2024

Citation: Zeng C, Yang J., et al., 2024. The Role of Dopamine D2 receptors and Oxidative Stress in the Pathogenesis of Hypertension. Medical Research Archives, [online] 12(4). https://doi.org/10.18103/mra.v12i4.5150

DOI: https://doi.org/10.18103/mra.v12i4.5150

ISSN: 2375-1924

RESEARCH ARTICLE

The Role of Dopamine D2 receptors and Oxidative Stress in the Pathogenesis of Hypertension

Chunyu Zeng[1], Jian Yang[2], Robin A Felder[3], Ines Armando[4], Pedro A Jose[4]*

[1]Chongqing Key Laboratory for Hypertension Research, Chongqing Cardiovascular Clinical Research Center, Chongqing Institute of Cardiology, Chongqing, P. R. China; chunyuzeng01@163.com

[2]Department of Clinical Nutrition, The Third Affiliated Hospital of Chongqing Medical University, Chongqing, P.R. China. yangjianac@163.com

[3]Department of Pathology, The University of Virginia, Charlottesville; raf7k@virginia.edu

[4]Division of Kidney Diseases and Hypertension, Department of Medicine, The George Washington School of Medicine and Health Sciences, Washington, DC, USA. Email; pjose@mfa.gwu.edu

*pjose@mfa.gwu.edu

ABSTRACT

Globally, hypertension is the number one risk factor for death, affecting more than 1 billion people. Hypertension is the result of the interactions among genetics, epigenetics, environment, and lifestyle. The long-term regulation of blood pressure rests on renal and non-renal mechanisms. The impaired renal sodium handling in hypertension is caused by aberrant counter-regulatory natriuretic/anti-natriuretic pathways. The sympathetic nervous and renin-angiotensin systems are anti-natriuretic pathways. A counter-regulatory natriuretic pathway is the renal dopaminergic system. Aberrant dopaminergic regulation of renal sodium transport in hypertension is caused by a decrease in renal dopamine synthesis and/or dysfunction of any of the 5 dopamine receptors (D1R, D2R, D3R, D4R, & D5R). Normally, an increase in sodium intake increases while a decrease in sodium intake decreases blood pressure, albeit transiently until sodium balance is achieved. However, ~50 % of hypertensive and ~26% of normotensive subjects have increased blood pressure on high sodium intake, a case of salt sensitivity, while ~20 % have increased blood pressure on a low sodium intake, a case of inverse salt sensitivity. Low and high sodium intakes are associated with increased incidence of cardiovascular events/mortality. In humans with inverse salt sensitivity, there is a linear relationship between the number of single nucleotide polymorphisms in DRD2 (rs6276 and 6277) and decreased renal D2R expression. The increase in blood pressure on a low sodium diet may be due to increased activities of the renin-angiotensin and sympathetic nervous systems that cannot be counteracted by D2R. Hypertension may be a cause or consequence of inflammation or oxidative stress. Deficient D2R function causes renal inflammation independently of the increase in blood pressure. Subjects carrying DRD2 single nucleotide polymorphisms have increased inflammation, mediated by decreased regulation of the miR-217-Wnt5a-Ror2 pathway. The D2R, via paraoxonase2 and sestrin2, maintains normal redox balance and blood pressure. In summary, the D2R is important in the maintenance of normal blood pressure by regulating renal sodium transport, vascular reactivity, inflammation, and redox balance.

Introduction

Globally, hypertension is the number one risk factor for death, affecting more than 1 billion people. Hypertension is the 13th leading cause of death in 2019[1] and the 12th leading cause of death in the US in 2021[2]. In 2019, essential hypertension and hypertensive renal disease were the 10th cause of deaths in non-Hispanic blacks and non-Hispanic Asians, 13th in Hispanics, and 14th in non-Hispanic whites[3]. Hypertension increases the risk for cardiovascular and renal diseases[4-6]. Hypertension is the result of the interactions among genetics, epigenetics, environment, and lifestyle[4-15]. Multiple genes influence an individual's blood pressure[12-20] and genetic risk scores for hypertension have been calculated[11,13,16,17].

The long-term regulation of blood pressure rests on non-renal and renal mechanisms[14,20-41]. The impaired renal handling of sodium in hypertension and salt sensitivity is caused by aberrant counter-regulatory natriuretic/anti-natriuretic pathways[14,21-40]. The sympathetic nervous system[4-6,39-49] and renin-angiotensin-aldosterone system (RAAS)[4-6,50-54] are anti-natriuretic pathways. A counter-regulatory natriuretic pathway is the renal dopaminergic system, aberrations of which cause hypertension [22,24,54-64]. In this article we reviewed the role of renal dopamine receptors, in particular the D2R, in the maintenance of normal blood pressure by regulating renal sodium transport, vascular reactivity, inflammation, and redox balance.

Role of G protein-coupled receptor kinase (GRK), GRK2, and GRK4 and dopamine in hypertension.

Dopamine is synthesized by the kidney[65-69], specifically by the renal proximal tubule (RPT)[24], and therefore, aberrant renal dopaminergic regulation of renal sodium transport in hypertension may be caused by a decrease in dopamine synthesis in the RPT[24,66-69]and/or dysfunction of any of the 5 dopamine receptor subtypes (D_1R, D_2R, D_3R, D_4R, & D_5R)[22,70-76]. Dysfunctions of D_1R and D_3R in hypertension are caused by their desensitization, due to increased GRK4 expression[71,77-79] in rodents, or GRK4 gene variants[23,50,80-92] in humans. GRK2, per se[93-95], or by impairing D_1R[71,79,96] is also involved in the pathogenesis of hypertension. The D2R is regulated by GRK2, GRK3, GRK5, and GRK6[97-101]. GRK4 is not in genome-wide association studies and hypertension, maybe because except for Illumina Human 1 M beadchip, not all the GRK4 variants are in the chips[82].

Salt sensitivity and Inverse Salt Sensitivity (ISS).

An increase in sodium intake usually increases while a decrease in sodium intake usually decreases blood pressure[4-6,11,24,25,37,39,54,57,58,61,62,73,75,78,81,84,102-106]. However, there are some humans whose blood pressures increase with a low sodium intake[106-121] and after acute waterloading[122]. The hypertensive effect of low sodium intake occurs in a minority of the hypertensive (11-28%) and normotensive (15-41%) human population, with an overall prevalence of 10-20%[119]. However, the prevalence of ISS is greater in those with normal than high BMI[119]. These would be the individuals who would be prescribed anti-hypertensive treatment and advised to decrease their sodium intake. In patients with ISS, their blood pressure would increase. Thus, the need to identify individuals with ISS, by genetic and clinical testing. A low sodium intake can also

be associated with increased incidence of cardiovascular events[116,121,123-126], chronic kidney disease[113,130], or mortality[116,125,126,127,128.129,130], in the presence or absence of vascular disease, diabetes, or hypertension. The association between low sodium intake and risk of cardiovascular disease or death remains after "extensive statistical adjustment for confounders and extensive efforts to avoid reverse causation[131]". ISS has also been reported to occur in non-genetically modified rodents. Sprague-Dawley rats with two kidneys[132-134] or one kidney[135,136] fed a low salt diet (0.04% NaCl or 0.004 +/-0.001 mEq sodium/gram body weight) also developed hypertension. Nonetheless, the existence of ISS continues to be disputed[137-140]. The increased mortality with low sodium intake can be counteracted by a high protein intake[128].

D2R salt sensitivity and ISS

In mammals, there are two D2R isoforms, *DRD2* short, *DRD2* long, the former is mainly presynaptic while the latter is mainly post-synaptic[141-143]. There are three D2R isoforms in teleosts[144]. The renal D2R isoform is the DRD2 long[145]. *DRD2* variants are associated with hypertension[55,146-148].

Germline deletion in the kidney of aromatic amino acid decarboxylase which synthesizes dopamine[24] or any of the dopamine receptor subtype genes[22,54,55,70,73,74,76,150,151], including *Drd2*[55,149,151-155], causes salt-sensitive hypertension[153]. Renal-selective *Drd2* silencing using *Drd2* siRNA also increases blood pressure, but salt sensitivity was not tested[70,149]. The D2R also regulates renal dopamine production; renal aminoacid decarboxylase activity is decreased in 20-30-week-old *Drd2-/-* mice[152]. Ozono et al reported that *Drd2-/-* mice fed 0.01% or 0.1% NaCl diet are normotensive, but blood pressure also increased when fed 4% NaCl diet, which was related to insufficient increase in sodium excretion[152,153]. The effect of mouse strain on salt sensitivity has to be taken into consideration. Ozono et al used C57Bl/6J x DBA/2J mice that were fed the diets for 8 weeks, starting at 6 weeks of age[152,153]. C57/Bl/6J mice have high catechol-o-methyl transferase activity whereas DBA/2J mice have low catechol-o-methyl transferase activity[156,157]. DBA/2J mice have been reported to develop salt-sensitive hypertension when they are fed a low magnesium diet[158]. C57Bl/6J mice may[159,160] or may not[161-164] have salt-sensitive hypertension, which may be strain-dependent[160]. It is also possible that age is a factor involved in ISS; in humans, younger than older individuals are more likely to have ISS while the converse is true for salt sensitivity[109,165]. Indeed, the ISS of blood pressure (increase in blood pressure on low salt diet and decrease in blood pressure on high salt diet) in Sprague-Dawley rats was manifested as early as 6 weeks of age[132]. The blood pressure of *Drd2*$^{-/-}$ mice can be influenced by sodium intake; high NaCl intake increases blood pressure that is normalized by a normal NaCl intake but increased again by a low sodium intake, a case of both salt sensitivity and ISS[166-171].

There is a linear relationship between the number of single nucleotide polymorphisms (SNPs) in the *DRD2* (rs6276 and 6277), and decreased expression in urine-derived renal proximal tubule cells in humans with ISS, suggesting the involvement of *DRD2*[170,171]. The D2R negatively interacts with angiotensin type 1 receptor (AT1R) in several tissues[172,173], other than the kidney, which may be related to D2R and AT1R heterodimerization, at least in the rat striatum[173]. The D2R also negatively

interacts with AT1R in the kidney[174], e.g., renal proximal tubule[149,155,175]. Dopamine[54,62,64,174-180], via D1R[62,63,181-183], D3R[73,184-187], D4R[74,186,188], and D5R[75,76,136,137], also interact with the renin-angiotensin system in the kidney. *DRD2* gene variants that decrease D2R expression and/or function impair the ability of the D2R to impede AT1R function and probably the α1-adrenergic receptor function[54], as seen in Sprague-Dawley rats which have ISS[132-136]. The hypertension in *Drd2*$^{-/-}$ mice on normal sodium diet (0.6% NaCl) is due to increased activity of the sympathetic nervous system[151,189] but not the renin-angiotensin system[151]. However, in rats fed a low sodium diet, the increase in blood pressure may not[133] or may be due to an increase in the renin-angiotensin system[43,132,134,135] and sympathetic activities[43,132], including an increase in renal nerve activity and norepinephrine content[135], but the genes involved in this process are not known.

D2R, inflammation, and oxidative stress

Dopamine and all its receptors in the kidney, as related to their role in maintaining normal blood pressure, also involves their ability to regulate inflammation[189-191] and prevent oxidative stress[192]. However, oxidative stress can also cause dopamine receptor, e.g., D1R, dysfunction[193]. Excessive stimulation of the D2-like but not D1-like receptors can also increase the production of reactive oxygen species[194]. High concentrations of dopamine (50-500 μM), via D2R can cause death of brain striatal neurons and peripheral blood lymphocytes that has been related to increased production of reactive oxygen species[195,196]. Low concentrations of dopamine (1-1000 nM) can also increase the production of reactive oxygen species in the mitochondria of opossum kidney cells[197]. However, a low concentration of dopamine (1 μM), via D1-like receptors, can also decrease the production of reactive oxygen species in peripheral blood lymphocytes[196]. Pharmacological studies have shown that D2-like receptors, D2R[195,198-202], D3R[198,200,203-206], and D4R[200,207-209] are protective of neurons, oligodendrocytes, mesencephalic cells, retina, vascular endothelial cells, and mouse, rat, and human renal proximal tubule cells against oxidative stress.

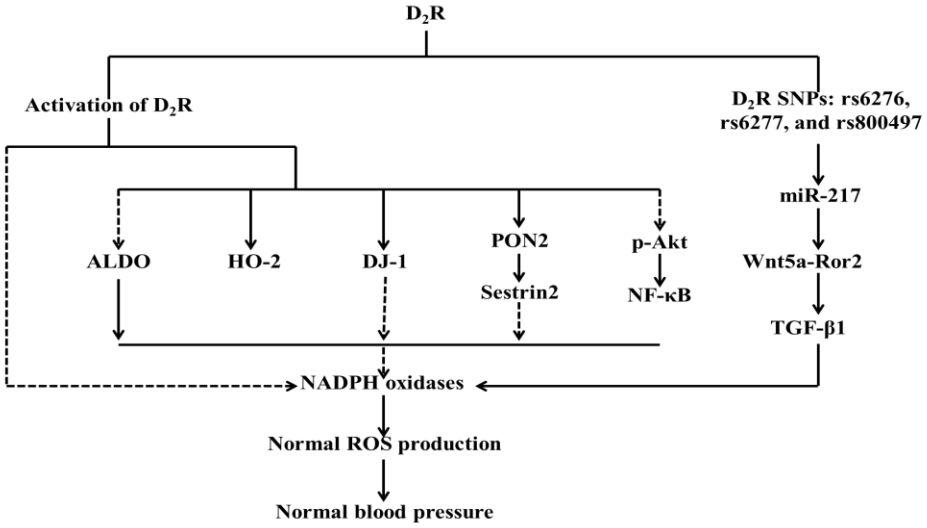
The D2R keeps the blood pressure in the normal range[151-155], in part by regulating renal inflammation[155], renal production of reactive oxygen species[154], and renal sodium handling[152]. Germline deletion of *Drd2* in mice results in enhanced vascular reactivity to α - adrenergic and ETB receptors but not to AT1R[210] but this is different from studies that have reported D2R and AT1R interaction in the kidney (renal proximal tubule cells[149], kidneys from obese rats[174] or kidneys after renal denervation[187]) and other tissues, such as the ventricular myocytes[172,] and brain striatum[173,211]. Germline deletion of *Drd2* in mice also causes reactive oxygen species-dependent hypertension[154]. The renal-selective silencing of *Drd2* by the renal subcapsular infusion of *Drd2* siRNA into the left kidney but not the right kidney in 8-10-week-old C57Bl/6J mice increased systolic and diastolic blood pressures[70]. The left renal-selective silencing of *Drd2* in right nephrectomized mice by the left ureteral infusion of AAV-9 carrying *Drd2* siRNA also increased their blood pressures. The lack of *Drd2* in the kidneys of these mice was associated with increased expression of proinflammatory and profibrotic factors and serum creatinine. The increased blood pressure and renal proinflammatory and pro-fibrotic factors were

mitigated or normalized by the rescue of *Drd2* with the retrograde ureteral infusion of AAV-9 virus carrying the normal *Drd2*. However, the role of oxidative stress in these experiments was not determined.

Oxidative stress has been shown to be important in the pathogenesis of hypertension[212-215]. This occurs when there is an imbalance in the production and quenching of reactive oxygen species. Reactive oxygen species are generated by the activity of NADPH oxidase, cyclooxygenases, xanthine oxidases, lipogenesis, iron-catalyzed Fenton reaction, and nitric oxide synthases[213]. NADPH oxidase is responsible for about half of the production of reactive oxygen species and the mitochondria is responsible for the remaining half, at least in the kidney[215]. It should be recognized, however, that normal generation of reactive oxygen species is important in cellular signal transduction[212].

As aforementioned, germline deletion of *Drd2* in mice causes reactive oxygen species-dependent hypertension[154]. The D2R keeps reactive oxygen species in "normal" state by increasing the activity of anti-oxidant enzymes, e.g., DJ-1[216], paraoxonase 2[217], and sestrin[218] and decreasing the activity of oxidant enzymes, i.e., NADPH oxidases[151,216,217] (**Figure**). There are seven NADPH oxidase homologs, four (Nox1, Nox 2, Nox4, and Nox5) are expressed in the vasculature and the kidney[219-222]; they are the major sources of reactive oxygen species[220,221]. Nox5 may be responsible for the oxidative stress in renal proximal tubules in human essential hypertension[222]. The neuroprotective effect of D2R has been reported to be related to DJ-1 (aka Park 7)[216]. The D2R normally regulates DJ-1 expression in renal proximal tubules cells[216]. The ability of D2R to regulate the production of reactive oxygen species is related, in part, to an increase in DJ-1 expression. Renal-selective silencing of *Dj-1* in mice increases Nox4 expression and NADPH oxidase activity, production of reactive oxygen species, and blood pressure.

Figure 1



Schematic representation of the role of renal D2R on the regulation of oxidative stress. The broken lines indicate inhibitory effects, whereas the solid lines indicate stimulatory effects. ALDO, aldosterone; D2R, dopamine D2 receptor; HO-2, heme oxygenase-2; NF-kB, nuclear factor-kB; NRF2=nuclear factor

erythroid factor 2-related factor 2; rs=reference SNP; SNP=single nucleotide polymorphism, SOD=superoxide dismutase, TGF-β1, transforming growth factor-beta 1 (adapted from Yang J, Villar VAM, Jose PA, et al. Renal Dopamine Receptors and Oxidative Stress: Role in Hypertension. Antioxid Redox Signal. 2021; 34(9):716-735. doi: 10.1089/ars.2020.8106).

The nuclear factor erythroid factor 2-related factor 2 (Nrf2), which by itself does not have antioxidative function[223], participates in the defense against oxidative stress in many tissues, including the kidney[224-226] by regulating the expression of several antioxidant genes[223], including NO[227]. Nrf2 is downstream of D2R and DJ-1[202,228-230]. DJ-1 is regulated by D2R[230]. DJ-1 induces superoxide dismutase 2 (SOD2) expression in the kidney[229]. SOD may be downstream of Nrf2[216]. SOD inhibits NADPH oxidase 5 in human renal proximal tubule cells, the expression of which is increased in hypertension[222]. In addition, germline deletion of *Drd2* in mice increases the expression of Nox1, Nox2, and Nox4[154]. Germline deletion of *Drd2* in mice increases blood pressure[151,210] that is salt-sensitive[152,153]. This may be related in part to the lack of impairment in the suppression of aldosterone secretion when D2R expression/function is impaired[154]; D2R is expressed in the adrenal zona glomerulosa[231] and germline deletion of *Drd2* increases aldosterone production[154]. Aldosterone secretion in humans can be negatively regulated by D2R agonists and *DRD2* expression the adrenal cortex is decreased in aldosterone-producing adenoma[231,232]. Aldosterone stimulates the production of reactive oxygen species by stimulating NADPH oxidase activity[233]. An aldosterone antagonist, spironolactone normalized the blood pressure and the production of reactive oxygen species but did not affect *Drd2* expression in $D2^{-/-}$ or $D2^{+/+}$ mice, indicating that the aldosterone effect is downstream of D2R[154].

Monoamine oxidase which catalyzes the degradation of dopamine to homovanillic acid[234] can also increase the production of reactive oxygen species[235] but not affected by dopamine receptors in the kidney[236]. Thus, dopamine can also induce oxidative stress, involving H2O2 produced by monoamine oxidase[237]. However, a reduction of dopamine catabolism by suppression of monoamine oxidase B which increases dopamine levels increases the activity of D2R and decreases the deleterious effects of reactive oxygen species[238]. Nitric oxide synthase activity can also be regulated by D2R[239,240]. Oxidative stress and nitric oxide deficiency have been linked to the pathogenesis of hypertension[241]. These pharmacological and rodent genetic studies related to the D2R have human relevance because as aforementioned, variants of *DRD2* are associated with human essential hypertension[55,146-148].

D2R SNPS and miR-217 pathway

Synonymous mutations in the human dopamine receptor D2 (*DRD2*) affect mRNA stability and synthesis of the receptor[242]. Several common single nucleotide polymorphisms (SNPs) of *DRD2* are associated with decreased D_2R expression/function, increased vulnerability to renal inflammation and injury[56]. *DRD2* rs6276, rs6277, and rs180047 (*Taq*1) are associated with increased blood pressure and hypertension[56,148]. *DRD2* rs7952106 and miR4301, that reside in an intron of DRD2 and can negatively regulate *DRD2* expression[243], are associated with increased systolic blood pressure in children with sickle cell disease[244,245].

D2R positively regulates the expression of miR-217; subjects carrying DRD2 SNPs that decrease D2R expression have increased inflammation (TGFβ1) that is related to decreased regulation of the miR-217-Wnt5a-Ror2 pathway. In the kidney, miR-217-5 mimic decreases the expression of TGFβ1[246]. In macrophages, miR-217 impairs activated STAT-1-induced inflammation and oxidative stress caused by smog-induced acute lung injury[247] and intestinal damage, related to oxidative stress in ducklings[248]. However, there are organ specific effects. For example, in the brain, miR-217 may increase inflammation and oxidative stress[249]. In septic lung injury, miR-217 also aggravates inflammation and oxidative stress[250].

Conclusion

Normally, an increase in sodium intake increases while a decrease in sodium intake decreases blood pressure, albeit transiently until sodium balance is achieved. However, ~50 % of hypertensive and ~26% of normotensive subjects have increased blood pressure on high sodium intake, a case of salt sensitivity, while ~20 % have increased blood pressure on a low sodium intake, a case of ISS. These individuals would be prescribed anti-hypertensive treatment and advised to decrease their sodium intake. However, in patients with ISS, their blood pressure would increase. Thus, the need to identify individuals with ISS, by genetic and clinical testing. In humans with ISS, there is a linear relationship between the number of SNPs in DRD2 (rs6276 and 6277) and decreased renal D2R expression. The increase in blood pressure in mice with decreased expression of D2R, e.g., *Drd2*$^{-/-}$ mice, on a low sodium diet may be due to an increase in the renin-angiotensin system and sympathetic activities. The ability of dopamine and all its receptors in the kidney to maintain a normal blood pressure also involves not only their ability to increase sodium excretion but also to regulate inflammation and prevent oxidative stress. The D2R keeps blood pressure and redox balance in the normal state by increasing the activity of anti-oxidant enzymes, such as DJ-1, paraoxonase 2, and sestrin2, and decreasing the activity of antioxidant enzymes, such as NADPH oxidase. Deficient D2R function can cause renal inflammation independently of high blood pressure. Subjects carrying DRD2 SNPs have increased inflammation that is mediated by decreased regulation of the miR-217-Wnt5a-Ror2 pathway. Thus, the D2R is important in the maintenance of normal blood pressure by regulating renal sodium transport, vascular reactivity, inflammation, and reactive oxygen species.

Author Contribution Statement:

All authors contributed equally to this review and have read and agreed to the published version of the manuscript.

Conflict of Interest Statement:

The authors declare no conflict of interest.

Acknowledgement Statement:

None

Funding Statement:

This research was funded in part by DK134574, DK119652, DK039308, HL068686, HL023081, HL092196, and HL074940 grants from the National Institute of Health, USA.

References:

1. https://world-heart-federation.org/what-we-do/hypertension/

2. Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality 2018-2021 on CDC WONDER Online Database, released in 2023. Data are from the Multiple Cause of Death Files, 2018-2021, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at http://wonder.cdc.gov/mcd-icd10-expanded.html on Aug 7, 2023, 12:25:01 PM

3. Heron M. Deaths: Leading Causes for 2019. *Natl Vital Stat Rep*. 2021;70(9):1-114.

4. Hall JE, Granger JP, do Carmo JM, et al. Hypertension: physiology and pathophysiology. *Compr Physiol*. 2012;2(4):2393-2442. doi: 10.1002/cphy.c110058.

5. Jung MH, Ihm SH. Obesity-related hypertension and chronic kidney disease: from evaluation to management. *Kidney Res Clin Pract*. 2023;42(4):431-444. doi: 10.23876/j.krcp.23.072.

6. Drury ER, Wu J, Gigliotti JC, Le TH. Sex Differences in Blood Pressure Regulation and Hypertension: Renal, Hemodynamic, and Hormonal Mechanisms. *Physiol Rev*. Physiol Rev. 2024;104(1):199-251. doi: 10.1152/physrev.00041.2022.

7. Hahad O, Rajagopalan S, Lelieveld J, et al. Noise and Air Pollution as Risk Factors for Hypertension: Part II-Pathophysiologic Insight. *Hypertension*. 2023;80(7):1384-1392. doi: 10.1161/HYPERTENSIONAHA.123.20617

8. Yin Y, Yu Z, Wang J, Sun J. Effects of the different Tai Chi exercise cycles on patients with essential hypertension: A systematic review and meta-analysis. *Front Cardiovasc Med*. 2023;10:1016629. doi: 10.3389/fcvm.2023.1016629.

9. Wattanapisit A, Ng CJ, Angkurawaranon C, Wattanapisit S, Chaovalit S, Stoutenberg M. Summary and application of the WHO 2020 physical activity guidelines for patients with essential hypertension in primary care. *Heliyon*. 2022;8(10):e11259. doi: 10.1016/j.heliyon.2022.e11259

10. Kokubo Y, Padmanabhan S, Iwashima Y, Yamagishi K, Goto A. Gene and environmental interactions according to the components of lifestyle modifications in hypertension guidelines. *Environ Health Prev Med*. 2019;24(1):19. doi: 10.1186/s12199-019-0771-2.

11. Nierenberg JL, Li C, He J, et al. Blood Pressure Genetic Risk Score Predicts Blood Pressure Responses to Dietary Sodium and Potassium: The GenSalt Study (Genetic Epidemiology Network of Salt Sensitivity). *Hypertension*. 2017;70(6):1106-1112. doi: 10.1161/HYPERTENSIONAHA.117.10108.

12. Osazuwa-Peters OL, Waken RJ, Schwander KL, et al. Identifying blood pressure loci whose effects are modulated by multiple lifestyle exposures. *Genet Epidemiol*. 2020;44(6):629-641. doi: 10.1002/gepi.22292.

13. Sun X, Pan Y, Zhang R, et al. Life-Course Associations between Blood Pressure-Related Polygenic Risk Scores and Hypertension in the Bogalusa Heart Study. *Genes (Basel)*. 2022;13 (8):1473. doi: 10.3390/genes13081473.

14. Arnett DK, Claas SA. Omics of Blood Pressure and Hypertension. *Circ Res*. 2018; 122(10):1409-1419. doi: 10.1161/CIRCRESAHA.118.311342

15. Wuttke M, Li Y, Li M, Sieber KB, et al. A catalog of genetic loci associated with kidney function from analyses of a million individuals. *Nat Genet.* 2019;51(6):957-972. doi: 10.1038/s41588-019-0407-x.

16. Pérez-Gimeno G, Seral-Cortes M, Sabroso-Lasa S, et al. Development of a genetic risk score to predict the risk of hypertension in European adolescents from the HELENA study. *Front Cardiovasc Med.* 2023;10:1118919.

17. Kurniansyah N, Goodman MO, Khan TK, et al. Evaluating the use of blood pressure polygenic risk scores across race/ethnic background groups. *Nat Commun.* 2023;14 (1):3202. doi: 10.3389/fcvm.2023.1118919.

18. Du B, Jia X, Tian W, et al. Associations of SUCNR1, GRK4, CAMK1D gene polymorphisms and the susceptibility of type 2 diabetes mellitus and essential hypertension in a northern Chinese Han population. *J Diabetes Complications.* 2021;35(1):107752. doi: 10.1016/j.jdiacomp.2020.107752.

19. Cipolletta E, Ciccarelli M, Izzo R, Finelli R, Trimarco B, Iaccarino G. A polymorphism within the promoter of the dopamine receptor D1 (DRD1 -48A/G) associates with impaired kidney function in white hypertensive patients. *Transl Med UniSa.* 2012;2:10-19.

20. Giri A, Hellwege JN, Keaton JM, et al. Trans-ethnic association study of blood pressure determinants in over 750,000 individuals. *Nat Genet.* 2019;51(1):51-62. doi: 10.1038/s41588-018-0303-9.

21. Davenport AP, Hyndman KA, Dhaun N, et al. Endothelin. *Pharmacol Rev.* 2016;68(2): 357-418. doi: 10.1124/pr.115.011833.

22. Albrecht FE, Drago J, Felder RA, et al. Role of the D1A dopamine receptor in the pathogenesis of genetic hypertension. *J Clin Invest.* 1996;97(10):2283-2288. doi: 10.1172/JCI118670.

23. Felder RA, Sanada H, Xu J, et al. G protein-coupled receptor kinase 4 gene variants in human essential hypertension. *Proc Natl Acad Sci USA.* 2002;99(6):3872-3877. doi: 10.1073/pnas.062694599.

24. Zhang MZ, Yao B, Wang S, et al. Intrarenal dopamine deficiency leads to hypertension and decreased longevity in mice. *J Clin Invest.* 2011;121(7):2845-2854. doi: 10.1172/JCI57324.

25. Carey RM, Schoeffel CD, Gildea JJ, et al. Salt sensitivity of blood pressure is associated with polymorphisms in the sodium-bicarbonate cotransporter. *Hypertension.* 2012;60(5):1359-1366. doi: 10.1161/HYPERTENSIONAHA.112.196071.

26. Titze J, Rakova N, Kopp C, Dahlmann A, Jantsch J, Luft FC. Balancing wobbles in the body sodium. *Nephrol Dial Transplant.* 2016; 31(7):1078-1081. doi: 10.1093/ndt/gfv343.

27. Laurent S, Boutouyrie P. The structural factor of hypertension: large and small artery alterations. *Circ Res.* 2015;116(6):1007-1021. doi: 10.1161/CIRCRESAHA.116.303596.

28. Dinh Cat AN, Friederich-Persson M, White A, Touyz RM. Adipocytes, aldosterone and obesity-related hypertension. *J Mol Endocrinol.* 2016;57(1):F7-21. doi: 10.1530/JME-16-0025.

29. Joyner MJ, Limberg JK. Blood pressure: return of the sympathetics? *Curr Hypertens Rep.* 2016;18(1):7. doi: 10.1007/s11906-015-0616-3.

30. Grassi G, Dell'Oro R, Quarti-Trevano F, Vanoli J, Oparil S. Sympathetic Neural Mechanisms in Hypertension: Recent Insights. *Curr Hypertens Rep.* 2023;25(10):263-270. doi: 10.1007/s11906-023-01254-4.

31. Cao W, Yang Z, Liu X, et al. A kidney-brain neural circuit drives progressive kidney damage and heart failure. *Signal Transduct Target Ther.* 2023;8(1):184. doi: 10.1038/s41392-023-01402-x.

32. Kosaki K, Park J, Matsui M, et al. Elevated urinary angiotensinogen excretion links central and renal hemodynamic alterations. *Sci Rep.* 2023;13(1):11518. doi: 10.1038/s41598-023-38507-w.

33. Yamaguchi H, Gomez RA, Sequeira-Lopez MLS. Renin Cells, From Vascular Development to Blood Pressure Sensing. *Hypertension.* 2023;80(8):1580-1589. doi: 10.1161/HYPERTENSIONAHA.123.20577.

34. Stec DE, Juncos LA, Granger JP. Renal intramedullary infusion of tempol normalizes the blood pressure response to intrarenal blockade of heme oxygenase-1 in angiotensin II-dependent hypertension. *J Am Soc Hypertens.* 2016;10(4):346-351. doi: 10.1016/j.jash.2016.01.023.

35. Kulthinee S, Tasanarong A, Franco M, Navar LG. Interaction of Angiotensin II AT1 Receptors with Purinergic P2X Receptors in Regulating Renal Afferent Arterioles in Angiotensin II-Dependent Hypertension. *Int J Mol Sci.* 2023;24(14):11413. doi: 10.3390/ijms241411413.

36. Sadri S, Tomar N, Yang C, Audi SH, Cowley AW Jr, Dash RK. Effects of ROS pathway inhibitors and NADH and $FADH_2$ linked substrates on mitochondrial bioenergetics and ROS emission in the heart and kidney cortex and outer medulla. *Arch Biochem Biophys.* 2023;744:109690. doi: 10.1016/j.abb.2023.109690.

37. Lu X, Crowley SD. Actions of Dendritic Cells in the Kidney during Hypertension. *Compr Physiol.* 2022;12(3):4087-4101. doi: 10.1002/cphy.c210050.

38. Yang T, Song C, Ralph DL, et al. Cell-Specific Actions of the Prostaglandin E-Prostanoid Receptor 4 Attenuating Hypertension: A Dominant Role for Kidney Epithelial Cells Compared With Macrophages. *J Am Heart Assoc.* 2022;11(19):e026581. doi: 10.1161/JAHA.122.026581.

39. Sánchez-Lozada LG, Madero M, et al. Sugar, salt, immunity and the cause of primary hypertension. *Clin Kidney J.* 2023;16(8):1239-1248. doi: 10.1093/ckj/sfad058.

40. Shekhar S, Varghese K, Li M, et al. Conflicting Roles of 20-HETE in Hypertension and Stroke. *Int J Mol Sci.* 2019;20(18):4500. doi: 10.3390/ijms20184500.

41. Wu X, Zhang N, Yu J, et al. The underlying mechanism of transcription factor IRF1, PRDM1, and ZNF263 involved in the regulation of NPPB rs3753581 on pulse pressure hypertension. *Gene.* 2023:878:147580. doi: 10.1016/j.gene.2023.147580.

42. Shinohara K, Liu X, Morgan DA, et al. Selective Deletion of the Brain-Specific Isoform of Renin Causes Neurogenic Hypertension. *Hypertension.* 2016;68(6):1385-1392. doi: 10.1161/HYPERTENSIONAHA.116.08242.

43. Drawz P, Baumann D, Dayton A. Renal denervation: recent developments in clinical and preclinical research. Curr Opin Nephrol Hypertens. 2023;32(5):404-411. doi: 10.1097/MNH.0000000000000908

44. Grassi G, Dell'Oro R, Quarti-Trevano F, et al. Sympathetic Neural Mechanisms in Hypertension: Recent Insights. *Curr Hypertens Rep.* 2023;25(10):263-270. doi: 10.1007/s11906-023-01254-4.

45. Sonalker PA, Jackson EK. Norepinephrine, via beta-adrenoceptors, regulates bumetanide -sensitive cotransporter type 1 expression in thick ascending limb cells. *Hypertension.* 2007;49(6):1351-1357. doi: 10.1161/HYPERTENSIONAHA.107.088732.

46. Richards EM, Li J, Stevens BR, Pepine CJ, Raizada MK. Gut Microbiome and Neuroinflammation in Hypertension. *Circ Res.* 2022;130(3):401-417. doi: 10.1161/CIRCRESAHA.121.319816.

47. Mahfoud F, Kandzari DE, Kario K, et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet.* 2022;399(10333): 1401-1410. doi: 10.1016/S0140-6736(22)00455-X.

48. Bhatt DL, Vaduganathan M, Kandzari DE, et al. Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial. *Lancet.* 2022;400 (10361):1405-1416. doi: 10.1016/S0140-6736(22)01787-1.

49. Osborn JW, Tyshynsky R, Vulchanova L. Function of Renal Nerves in Kidney Physiology and Pathophysiology. *Annu Rev Physiol.* 202; 83:429-450. doi: 10.1146/annurev-physiol-031620-091656.

50. Wang Z, Zeng C, Villar VA, et al. Human GRK4γ142V variant promotes angiotensin II type I receptor-mediated hypertension via renal histone deacetylase type 1 inhibition. *Hypertension.* 2016;67(2):325-334. doi: 10.1161/HYPERTENSIONAHA.115.05962.

51. Okuno K, Torimoto K, Cicalese SM, et al. Angiotensin II Type 1A Receptor Expressed in Smooth Muscle Cells is Required for Hypertensive Vascular Remodeling in Mice Infused With Angiotensin II. *Hypertension.* 2023;80(3):668-677. doi: 10.1161/HYPERTENSIONAHA.122.20601.

52. Kulthinee S, Tasanarong A, Franco M, Navar LG. Interaction of Angiotensin II AT1 Receptors with Purinergic P2X Receptors in Regulating Renal Afferent Arterioles in Angiotensin II-Dependent Hypertension. *Int J Mol Sci.* 2023;24(14):11413. doi: 10.3390/ijms241411413.

53. Nwia SM, Leite APO, Li XC, Zhuo JL. Sex differences in the renin-angiotensin-aldosterone system and its roles in hypertension, cardiovascular, and kidney diseases. *Front Cardiovasc Med. 2023*;10:1198090. doi: 10.3389/fcvm.2023.1198090.

54. Vaz de Castro PAS, Jose PA, Simões E Silva AC. Interactions between the intrarenal dopaminergic and the renin-angiotensin systems in the control of systemic arterial pressure. *Clin Sci (Lond).* 2022;136(16):1205-1227. doi: 10.1042/CS20220338.

55. Fang YJ, Thomas GN, Xu ZL, Fang J-Q, Critchley JAJH, Tomlinson B. An affected pedigree member analysis of linkage between the dopamine D2 receptor gene TaqI polymorphism and obesity and hypertension. *Int J Cardiol.* 2005;102(1):111-116. doi: 10.1016/j.ijcard.2004.05.010.

56. Jiang X, Konkalmatt P, Yang Y, et al. Single-nucleotide polymorphisms of the dopamine D2 receptor increase inflammation and fibrosis in human renal proximal tubule cells. *Hypertension.* 2014;63(3):e74-80. doi: 10.1161/HYPERTENSIONAHA.113.02569.

57. Chrysant SG. The Interaction of Kidneys and Gut in Development of Salt-Sensitive Hypertension. *Cardiol Rev.* 2023 Jun 5. doi: 10.1097/CRD.0000000000000518.

58. Thomas GN, Critchley JA, Tomlinson B, Cockram CS, Chan JC. Relationships between the taqI polymorphism of the dopamine D2 receptor and blood pressure in hyperglycaemic and normoglycaemic Chinese subjects. *Clin Endocrinol (Oxf).* 2001;55(5):605-11. doi: 10.1046/j.1365-2265.2001.01404.x.

59. Yang J, Hall JE, Jose PA, et al. Comprehensive insights in GRK4 and hypertension: From mechanisms to potential therapeutics. *Pharmacol Ther.* 2022;239: 108194. doi: 10.1016/j.pharmthera.2022.108194.

60. Zeng C, Xia T, Zheng S, Liang L, Chen Y. Synergistic Effect of Uroguanylin and D1 Dopamine Receptors on Sodium Excretion in Hypertension. *J Am Heart Assoc. 2022*;11 (6):e022827. doi: 10.1161/JAHA.121.022827.

61. Banday AA, Lokhandwala MF. Renal Dopamine Oxidation and Inflammation in High Salt Fed Rats. *J Am Heart Assoc.* 2020;9(1):e014977.
doi: 10.1161/JAHA.119.014977.

62. Olivares-Hernández A, Figuero-Pérez L, Cruz-Hernandez JJ, Sarmiento RG, Usagui-Martin R, Miramontes-Gonzales JP. Dopamine Receptors and the Kidney: An Overview of Health- and Pharmacological-Targeted Implications. *Biomolecules.* 2021;11(2):254. doi: 10.3390/biom11020254.

63. Gildea JJ, Xu P, Kemp BA, Carey RM, Jose PA, Felder RA. The Dopamine D1 Receptor and Angiotensin II Type-2 Receptor are Required for Inhibition of Sodium Transport Through a Protein Phosphatase 2A Pathway. *Hypertension.* 2019;73(6):1258-1265. doi: 10.1161/HYPERTENSIONAHA.119.12705.

64. Natarajan AR, Eisner GM, Armando I, et al. The Renin-Angiotensin and Renal Dopaminergic Systems Interact in Normotensive Humans. *J Am Soc Nephrol.* 2016;27(1):265-79. doi: 10.1681/ASN.2014100958. Epub 2015

65. Grossman E, Hoffman A, Tamrat M, Armando I, Keiser HR, Goldstein DS. Endogenous dopa and dopamine responses to dietary salt loading in salt-sensitive rats. *J Hypertens.* 1991;9(3):259-63.
doi: 10.1097/00004872-199103000-00010.

66. Jiang X, Zhang Y, Yang Y, et al. Gastrin stimulates renal dopamine production by increasing the renal tubular uptake of l-DOPA. *Am J Physiol Endocrinol Metab.* 2017;312(1): E1-E10.

67. Pinto V, Pinho MJ, Soares-da-Silva P. Renal amino acid transport systems and essential hypertension. FASEB J. 2013;27(8): 2927-38.

68. Hsin Y-H, Tang C-H, Lai H-T, et al. The role of TonEBP in regulation of AAD expression and dopamine production in renal proximal tubule cells upon hypertonic challenge. *Biochem Biophys Res Commun.* 2011;414(3):598-603.

69. Baines AD, Drangova R, Hatcher C. Dopamine production by isolated glomeruli and tubules from rat kidneys. *Can J Physiol Pharmacol.* 1985;63(2):155-8.

70. Konkalmatt PR, Asico LD, Zhang Y, et al. Renal rescue of dopamine D2 receptor function reverses renal injury and high blood pressure. JCI Insight. 2016;1(8):e85888.

71. Trivedi M, Lokhandwala MF. Rosiglitazone restores renal D1A receptor-Gs protein coupling by reducing receptor hyperphosphorylation in obese rats. *Am J Physiol Renal Physiol.* 2005;289(2):F298-304.

72. Miramontes-Gonzalez JP, Hightower CM, Zhang K, et al. A new common functional coding variant at the DDC gene change renal

enzyme activity and modify renal dopamine function. *Sci Rep.* 2019;9(1):5055.

73. Asico LD, Ladines C, Fuchs S, et al. Disruption of the dopamine D3 receptor gene produces renin-dependent hypertension. *J Clin Invest.*1998;102(3):493-498.

74. Bek MJ, Wang X, Asico LD, et al. Angiotensin-II type 1 receptor-mediated hypertension in D4 dopamine receptor-deficient mice. *Hypertension.* 2006 Feb;47 (2):288-95.

75. Liu X, Wang W, Chen W, et al. Regulation of blood pressure, oxidative stress and AT1R by high salt diet in mutant human dopamine D5 receptor transgenic mice. *Hypertens Res.* 2015;38(6):394-9.

76. Hollon TR, Bek MJ, Lachowicz JE, et al. Mice lacking D5 dopamine receptors have increased sympathetic tone and are hypertensive. *J Neurosci.* 2002;22(24):10801-10.

77. Villar VA, Jones JE, Armando I, et al. G protein-coupled receptor kinase 4 (GRK4) regulates the phosphorylation and function of the dopamine D3 receptor. *J Biol Chem.* 2009;284(32):21425-1434.

78. Lu X, Ye Z, Zheng S, et al . Long-Term Exposure of Fine Particulate Matter Causes Hypertension by Impaired Renal D1 Receptor-Mediated Sodium Excretion via Upregulation of G-Protein-Coupled Receptor Kinase Type 4 Expression in Sprague-Dawley Rats. *J Am Heart Assoc.* 2018;7(1):e007185.

79. Wang X, Luo H, Chen C, et al. Prenatal lipopolysaccharide exposure results in dysfunction of the renal dopamine D1 receptor in offspring. *Free Radic Biol Med.* 2014;76:242-250.

80. Allen SJ, Parthasarathy G, Darke PL, et al. Structure and function of the hypertension variant A486V of G protein-coupled receptor kinase 4. *J Biol Chem.* 2015;290(33):20360-20373.

81. Padmanabhan S, Caulfield M, Dominiczak AF. Genetic and molecular aspects of hypertension. *Circ Res.* 2015;116(6):937-959.

82. Sanada H, Yoneda M, Yatabe J, et al. Common variants of the G protein-coupled receptor type 4 are associated with human essential hypertension and predict the blood pressure response to angiotensin receptor blockade. *Pharmacogenomics J.* 2016;16(1):3-9.

83. Zhang H, Sun ZQ, Liu SS, et al. Association between GRK4 and DRD1 gene polymorphisms and hypertension: a meta-analysis. *Clin Interv Aging.* 2015;11:17-27.

84. Rayner B, Ramesar R. The importance of G protein-coupled receptor kinase 4 (GRK4) in pathogenesis of salt sensitivity, salt sensitive hypertension and response to antihypertensive treatment. *Int J Mol Sci.* 2015;16(3):5741-5749.

85. Muskalla AM, Suter PM, Saur M, et al. G-protein receptor kinase 4 polymorphism and response to antihypertensive therapy. *Clin Chem.* 2014;60(12):1543-1548.

86. Bhatnagar V, O'Connor DT, Brophy VH, et al. G-protein-coupled receptor kinase 4 polymorphisms and blood pressure response to metoprolol among African Americans: sex-specificity and interactions. *Am J Hypertens.* 2009;22(3):332-8.

87. Vandell AG, Lobmeyer MT, Gawronski BE, et al. G protein receptor kinase 4 polymorphisms: β-blocker pharmacogenetics and treatment-related outcomes in hypertension. *Hypertension.* 2012;60(4):957-64.

88. Lee M, Kim MK, Kim SM, et al. Gender-based differences on the association between

salt-sensitive genes and obesity in Korean children aged between 8 and 9 years. PLoS One. 2015;10(3):e0120111.

89. Kimura L, Angeli CB, Auricchio MT, et al. Multilocus family-based association analysis of seven candidate polymorphisms with essential hypertension in an African-derived semi-isolated Brazilian population. *Int J Hypertens.* 2012;2012:859219.

90. Liu C, Xi B. Pooled analyses of the associations of polymorphisms in the GRK4 and EMILIN1 genes with hypertension risk. *Int J Med Sci.* 2012;9(4):274-9.

91. Watanabe H, Xu J, Bengra C, et al. Desensitization of human renal D1 dopamine receptors by G protein-coupled receptor kinase 4. *Kidney Int.* 2002;62(3):790-8.

92. Jiang W, Wang X, Li R, et a; Targeted capture sequencing identifies genetic variations of GRK4 and RDH8 in Han Chinese with essential hypertension in Xinjiang. *PLoS One.* 2021;16(7):e0255311.

93. Cohn HI, Xi Y, Pesant S, et al. G protein-coupled receptor kinase 2 expression and activity are associated with blood pressure in black Americans. *Hypertension.* 2009;54(1): 71-76.

94. Tutunea-Fatan E, Caetano FA, Gros R, et al. GRK2 targeted knock-down results in spontaneous hypertension and altered vascular GPCR signaling. *J Biol Chem.* 2015; 290(8):5141-5155.

95. Gros R, Benovic JL, Tan CM, et al. G-protein-coupled receptor kinase activity is increased in hypertension. *J Clin Invest.* 1997;99(9):2087-2093.

96. Banday AA, Fazili FR, Lokhandwala MF. Insulin causes renal dopamine D1 receptor desensitization via GRK2-mediated receptor phosphorylation involving phosphatidylinositol 3-kinase and protein kinase C. *Am J Physiol Renal Physiol.* 2007; 293(3):F877-884.

97. Daigle TL, Ferris MJ, Gainetdinov RR, et al. Selective deletion of GRK2 alters psychostimulant-induced behaviors and dopamine neurotransmission. *Neuropsychopharmacology.* 2014;39(10):2450-2462.

98. Ito K, Haga T, Lameh J, et al. Sequestration of dopamine D2 receptors depends on coexpression of G-protein-coupled receptor kinases 2 or 5. *Eur J Biochem.* 1999;260(1): 112-9.

99. Iwata K, Ito K, Fukuzaki A, et al. Dynamin and Rab5 regulate GRK2-dependent internalization of dopamine D2 receptors. *Eur J Biochem.* 1999;263(2):596-602.

100. Namkung Y, Dipace C, Javitch JA, Sibley DR. G protein-coupled receptor kinase-mediated phosphorylation regulates post-endocytic trafficking of the D2 dopamine receptor. *J Biol Chem.* 2009;284(22):15038-15051. doi: 10.1074/jbc.M900388200.

101. Crawford CA, Teran A, Ramirez GI, et al. Age-dependent effects of dopamine receptor inactivation on cocaine-induced behaviors in male rats: evidence of dorsal striatal D2 receptor supersensitivity. *J Neurosci Res.* 2019;97 (12):1546-1558. doi: 10.1002/jnr.24491.

102. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/ APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association task force on clinical practice

guidelines. *Hypertension.* 2018;71(6):1269-1324. doi: 10.1161/HYP.0000000000000066.

103. Burnier M, Monod M, Chiolero A, Maillard M, Nussberger J, Brunner HR. Renal sodium handling in acute and chronic salt loading/depletion protocols: the confounding influence of acute water loading. *J Hypertens.* 2000;18(11):1657-1664. doi: 10.1097/00004872-200018110-00018.

104. Harrison DG, Coffman TM, Wilcox CS. Pathophysiology of Hypertension: The Mosaic Theory and Beyond. *Circ Res.* 2021;128(7):847-863. doi: 10.1161/CIRCRESAHA.121.318082.

105. Dimsdale JE, Ziegler M, Mills P, Berry C. Prediction of salt sensitivity. *Am J Hypertens.* 1990;3(6 Pt 1):429-35.

106. Castiglioni P, Parati G, Lazzeroni D, et al. Hemodynamic and autonomic response to different salt intakes in normotensive individuals. *J Am Heart Assoc.* 2016;5(8):e003736. doi: 10.1161/JAHA.116.003736.

107. Overlack A, Ruppert M, Kolloch R, et al. Divergent hemodynamic and hormonal responses to varying salt intake in normotensive subjects. *Hypertension.* 1993;22(3):331-338. doi: 10.1161/01.hyp.22.3.331.

108. MacFadyen RJ, Lees KR, Reid JL. Responses to low dose intravenous perindoprilat infusion in salt deplete/salt replete normotensive volunteers. *Br J Clin Pharmacol.* 1994;38(4):329-334. doi: 10.1111/j.1365-2125.1994.tb04362.x.

109. Overlack A, Ruppert M, Kolloch R, Kraft K, Stumpe KO. Age is a major determinant of the divergent blood pressure responses to varying salt intake in essential hypertension. *Am J Hypertens.* 1995;8(8):829-836. doi: 10.1016/0895-7061(95)00213-9.

110. Longworth DL, Drayer JI, Weber MA, et al. Divergent blood pressure responses during short-term sodium restriction in hypertension. *Clin Pharmacol Ther.* 1980;27(4):544-6.

111. Mente A, O'Donnell MJ, Rangarajan S, et al. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med.* 2014;371:601-611. doi: 10.1056/NEJMoa1311989.

112. Montasser ME, Douglas JA, Roy-Gagnon M-H, et al. Determinants of Blood Pressure Response to Low Salt Intake in a Healthy Adult Population. *J Clin Hypertens* (Greenwich). 2011;13(11):795–800. doi: 10.1111/j.1751-7176.2011.00523.x

113. Yoon C-Y, Noh J, Lee J, et al. High and low sodium intakes are associated with incident chronic kidney disease in patients with normal renal function and hypertension. Kidney Int. 2018;93(4):921-931. doi: 10.1016/j.kint.2017.09.016.

114. Gildea JJ, Xu P, Schiermeyer KA, et al. Inverse Salt Sensitivity of Blood Pressure Is Associated with an Increased Renin-Angiotensin System Activity. *Biomedicines.* 2022;10(11):0. doi: 10.3390/biomedicines10112811.

115. Xu P, Sudarikova AV, Ilatovskaya DV, et al. Epithelial Sodium Channel Alpha Subunit (αENaC) Is Associated with Inverse Salt Sensitivity of Blood Pressure. *Biomedicines.* 2022;10(5):981. doi: 10.3390/biomedicines10050981.

116. Lamelas PM, Mente A, Diaz R, et al. Association of Urinary Sodium Excretion With Blood Pressure and Cardiovascular Clinical Events in 17,033 Latin Americans. *Am J Hypertens.* 2016;29(7):796-805. doi: 10.1093/ajh/hpv195.

117. Miller JZ, Weinberger MH, Daugherty SA, Fineberg NS, Christian JC, Grim CE. Heterogeneity of blood pressure response to dietary sodium restriction in normotensive adult. *J Chronic Dis*. 1987;40(3):245-250. doi: 10.1016/0021-9681(87)90160-3.

118. Alderman MH, Lamport B. Moderate sodium restriction. Do the benefits justify the hazards? *Am J Hypertens*. 1990;3(6 Pt 1):499-504. doi: 10.1093/ajh/3.6.499.

119. Romberger NT, Stock JM, Patik JC, et al. Inverse salt sensitivity in normotensive adults: role of demographic factors. *J Hypertens*. 2023;41(6):934-940.

120. He J, Huang J-F, Li C, et al. Sodium sensitivity, sodium resistance, and incidence of hypertension: a longitudinal follow-up study of dietary sodium intervention. *Hypertension* 2021;78(1):155-164.
doi: 10.1161/HYPERTENSIONAHA.120.16758.

121. Cuka E, Simoni M, Lanzani C, et al. Inverse salt sensitivity: an independent risk factor for cardiovascular damage in essential hypertension. *J Hypertens*. 2022;40(8):1504-1512. doi: 10.1097/HJH.0000000000003174.

122. Burnier M, Monod M, Chiolero A, et al. Renal sodium handling in acute and chronic salt loading/depletion protocols: the confounding influence of acute water loading. *J Hypertens*. 2000;18(11):1657-1664. doi: 10.1097/00004872-200018110-00018

123. O'Donnell MJ, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA*. 2011; 306(20):2229-2238. doi: 10.1001/jama.2011.1729.

124. Braam B, Huang X, Cupples WA, Hamza SM. Understanding the two faces of low-salt intake. *Curr Hypertens Rep*. 2017;19(6):49. doi: 10.1007/s11906-017-0744-z.

125. O'Donnell M, Mente A, Rangarajan S, et al. Joint association of urinary sodium and potassium excretion with cardiovascular events and mortality: prospective cohort study. *BMJ*. 2019;364:l772.
doi: 10.1136/bmj.l772.

126. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371(7):612-23.
doi: 10.1056/NEJMoa1311889.

127. Graudal N, Jurgens G, Baslund G, Alderman MH. Compared With Usual Sodium Intake, Low- and Excessive Sodium Diets Are Associated With Increased Mortality: A Meta-Analysis. *Am J Hypertens*. 2014;27(9):1129-1137. doi: 10.1093/ajh/hpu028.

128. Hessels NR, Zhu Y, Bakker SJL, de Borst MH, Navis GJ, Riphagen IJ. Low Sodium Intake, Low Protein Intake, and Excess Mortality in an Older Dutch General Population Cohort: Findings in the Prospective Lifelines-MINUTHE Study. *Nutrients*. 2023;15(2): 428. doi: 10.3390/nu15020428.

129. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. *JAMA*. 2011;305(17):1777-1785.
doi: 10.1001/jama.2011.574

130. Thomas MC, Moran J, Forsblom C, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care*. 2011;34(4) :861-866. doi: 10.2337/dc10-1722.

131. Mente A, O'Donnell M, Yusuf S. Sodium Intake and Health: What Should We Recommend Based on the Current Evidence? *Nutrients*. 2021;13(9):3232. doi: 10.3390/nu13093232.

132. Wang J, Deng Y, Zou X, et al. Long-term low salt diet increases blood pressure by activation of the renin-angiotensin and sympathetic nervous systems. *Clin Exp Hypertens.* 2019;41(8):739-746. doi: 10.1080/10641963.2018.1545850

133. Ott CE, Welch WJ, Lorenz JN, Whitescarver SA, Kotchen TA. Effect of salt deprivation on blood pressure in rats. *Am J Physiol.* 1989;256(5 Pt 2):H1426-1431. doi: 10.1152/ajpheart.1989.256.5.H1426

134. Webb DJ, Clark SA, Brown WB, et al. Dietary sodium deprivation raises blood pressure in the rat but does not produce irreversible hyperaldosteronism. *J Hypertens.* 1987;5(5):525-531. doi: 10.1097/00004872-198710000-00003.

135. Vari RC, Freeman RH, Davis JO, Sweet WD. Role of renal nerves in rats with low-sodium, one-kidney hypertension. *Am J Physiol.* 1986;250(2 Pt 2):H189-194. doi: 10.1152/ajpheart.1986.250.2.H189

136. Seymor AA, Davis JO, Freeman RH, et al. Hypertension produced by sodium depletion and unilateral nephrectomy: a new experimental model. *Hypertension.* 1980;2(2): 125-129. doi: 10.1161/01.hyp.2.2.125.

137. Cook NR, Appel LJ, Whelton PK. Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention. *J Am Coll Cardiol.* 2016;68(15): 1609-1617. doi: 10.1016/j.jacc.2016.07.745

138. Cappuccio FP, Beer M, Strazzullo P; European Salt Action Network. Population dietary salt reduction and the risk of cardiovascular disease. A scientific statement from the European Salt Action Network. *Nutr Metab Cardiovasc Dis.* 2018;29(2):107-114. doi: 10.1016/j.numecd.2018.11.010.

139. Cappuccio FP. Campbell NRC, He FJ, et al. Sodium and Health: Old Myths and a Controversy Based on Denial. *Curr Nutr Rep.* 2022;11(2):172-184. doi: 10.1007/s13668-021-00383-z.

140. Oparil S. Low sodium intake - cardiovascular health benefit or risk? *N Engl J Med.* 2014;371(7):677-679. doi: 10.1056/NEJMe1407695.

141. Lindgren N, Usiello A, Goiny M, et al. Distinct roles of dopamine D2L and D2S receptor isoforms in the regulation of protein phosphorylation at presynaptic and postsynaptic sites. *Proc Natl Acad Sci USA.* 2003;100(7):4305-4309. doi: 10.1073/pnas.0730708100.

142. Li L, Cheng L, Wang Y. Differential roles of two isoforms of dopamine D2 receptors in l-dopa-induced abnormal involuntary movements in mice. *Neuroreport.* 2021;32 (7):555-561. doi: 10.1097/WNR.0000000000001623

143. Cokkan KB, Mavri M. Rutland CS, et al. Critical Impact of Different Conserved Endoplasmic Retention Motifs and Dopamine Receptor Interacting Proteins (DRIPs) on Intracellular Localization and Trafficking of the D2 Dopamine Receptor (D2-R) Isoforms. *Biomolecules.* 2020;10(10):1355. doi: 10.3390/biom10101355.

144. Fontaine R, Affaticati P, Yamamoto K, et al. Dopamine inhibits reproduction in female zebrafish (Danio rerio) via three pituitary D2 receptor subtypes. *Endocrinology.* 2013;154 (2):807-818. doi: 10.1210/en.2012-1759.

145. Gao DQ, Canessa LM, Mouradian MM, Jose PA. Expression of the D2 subfamily of dopamine receptor genes in kidney. *Am J*

Physiol. 1994;266(4 Pt 2):F646-50. doi: 10.1152/ajprenal.1994.266.4.F646.

146. Rosmond R, Rankinen T, Chagnon M, et al. Polymorphism in exon 6 of the dopamine D(2) receptor gene (DRD2) is associated with elevated blood pressure and personality disorders in men. *J Hum Hypertens.* 2001; 15(8):553-558. doi: 10.1038/sj.jhh.1001231.

147. Bhatnagar P, Barron-Casella E, Bean CJ, et al. Genome-wide meta-analysis of systolic blood pressure in children with sickle cell disease. *PLoS One*. 2013;8(9):e74193. doi: 10.1371/journal.pone.0074193.

148. Thomas GN, Tomlinson B, Critchley JA. Modulation of blood pressure and obesity with the dopamine D2 receptor gene TaqI polymorphism. *Hypertension.* 2000;36(2): 177-182. doi: 10.1161/01.hyp.36.2.177

149. Zhang Y, Cuevas S, Asico LD, et al. Deficient dopamine D2 receptor function causes renal inflammation independently of high blood pressure. *PLoS One*. 2012;7(6): e38745

150. Asico L, Zhang X, Jiang J, et al. Lack of renal dopamine D5 receptors promotes hypertension. *J Am Soc Nephrol*. 2011;22(1): 82-89. doi: 10.1681/ASN.2010050533.

151. Armando I, Asico LD, Wang X, et al. Antihypertensive effect of etamicastat in dopamine D2 receptor-deficient mice. *Hypertens Res.* 2018;41(7):489-498. doi: 10.1038/s41440-018-0041-5.

152. Ozono R, Ueda A, Oishi Y, et al. Dopamine D2 receptor modulates sodium handling via local production of dopamine in the kidney. *J Cardiovasc Pharmacol.* 2003;42 Suppl 1:S75-79. doi: 10.1097/00005344-200312001-00017

153. Ueda A, Ozono R, Oshima T, et al. Disruption of the type 2 dopamine receptor gene causes a sodium-dependent increase in blood pressure in mice. *Am J Hypertens* 2003;16(10):853-858. doi: 10.1016/s0895-7061(03)01013-6.

154. Armando I, Wang X, Villar VA, et al. Reactive oxygen species-dependent hypertension in dopamine D2 receptor-deficient mice. *Hypertension.* 2007;49(3):672-678. doi: 10.1161/01.HYP.0000254486.00883.3d.

155. Zhang Y, Cuevas S, Asico LD, et al. Deficient dopamine D2 receptor function causes renal inflammation independently of high blood pressure. *PLoS One.* 2012;7(6): e38745. doi: 10.1371/journal.pone.0038745

156. Schlesinger K, Harkins J, Deckard BS, Paden C. Catechol-O-methyl transferase and monoamine oxidase activities in brains of mice susceptible and resistant to audiogenic seizures. *J Neurobiol.* 1975;6(6):587-96. doi: 10.1002/neu.480060605.

157. Eleftheriou BE. Regional brain catechol-O-methyl transferase: age related differences in the mouse. *Exp Aging Res.* 1975;1(1):99-103. doi: 10.1080/03610737508257951.

158. Kumagi A, Takeda S, Sohara E, et al. Dietary Magnesium Insufficiency Induces Salt-Sensitive Hypertension in Mice Associated With Reduced Kidney Catechol-O-Methyl Transferase Activity . *Hypertension.* 2021;78 (1):138-150. doi: 10.1161/HYPERTENSIONAHA.120.16377.

159. Escano CS, Armando I, Wang X, et al. Renal dopaminergic defect in C57Bl/6J mice. *Am J Physiol Regul Integr Comp Physiol.* 2009;297(6):R1660-1669. doi: 10.1152/ajpregu.00147.2009.

160. Combe R, Mudgett J, El Fertak L, et al. How does circadian rhythm impact salt sensitivity of blood pressure in mice? A study in two close C57Bl/6 substrains. *PLoS One.* 2016;11(4):e0153472. doi: 10.1371/journal.pone.0153472

161. Athirakul K, Kim HS, Audoly LP, Smithies O, Coffman TM. Deficiency of COX-1 causes natriuresis and enhanced sensitivity to ACE inhibition. *Kidney Int.* 2001;60(6):2324-9. doi: 10.1046/j.1523-1755.2001.00072.x

162. Kopkan L, Hess A, Husková Z, Cervenka L, Navar LG, Majid DS. High-salt intake enhances superoxide activity in eNOS knockout mice leading to the development of salt sensitivity. *Am J Physiol Renal Physiol.* 2010;299(3):F656-F663. doi: 10.1152/ajprenal.00047.2010.

163. Mangrum AJ, Gomez RA, Norwood VF. Effects of AT(1A) receptor deletion on blood pressure and sodium excretion during altered dietary salt intake. *Am J Physiol Renal Physiol.* 2002;283(3):F447–F453. doi: 10.1152/ajprenal.00259.2001.10.

164. Hartner A, Cordasic N, Klanke B, et al. Strain differences in the development of hypertension and glomerular lesions induced by deoxycorticosterone acetate salt in mice. *Nephrol Dial Transplant.* 2003;18(10):1999-2004. doi: 10.1093/ndt/gfg299.

165. Luft FC, Miller JZ, Grim CE, et al. Salt sensitivity and resistance of blood pressure. Age and race as factors in physiological responses. *Hypertension.* 1991;17(1 Suppl): I102-8. doi: 10.1161/01.hyp.17.1_suppl.i102.

166. Moore SC, Campisi R, Asico LD, Kumar M, Jose PA, Armando I. The renal mechanisms involved in the response to salt intake are sex related in mice. *Hypertension* 2023;80:AP383 /doi.org/10.1161/hyp.80.suppl_1.P383

167. Asico LD, Moore S, Jose PA, Armando I. Deletion of the dopamine D2 receptor in the renal proximal tubule increases blood pressure on low salt diet and decreases blood pressure on high salt diet, a case of inverse salt sensitivity. 2021 *Kidney Week* (Moderated Poster session). PO1814.

168. Gildea JJ, Xu P, Schiermeyer K, Yue W, Carey RM, Jose PA, Felder RA. The etiology of inverse salt sensitivity of blood pressure: miRNA-485-5p binds to the dopamine type 2 receptor (D2R) snp rs6276 and decreases D2R expression. *Hypertension* 2020;76(Suppl 1): A12. 10.1161/hyp.76.suppl_1.12 (oral presentation).

169. Felder RA, Gildea JJ, Xu P, Yue W, Armando I, Carey RM, Jose PA. Inverse Salt Sensitivity of Blood Pressure: Mechanisms and Potential Relevance for Prevention of Cardiovascular Disease. *Curr Hypertens Rep* 24(9):361-374, 2022. doi: 10.1007/s11906-022-01201-9.

170. Gildea JJ, Xu P, Schiermeyer KA, et al Inverse Salt Sensitivity of Blood Pressure Is Associated with an Increased Renin-Angiotensin System Activity. *Biomedicines.* 2022;10(11):0. doi: 10.3390/biomedicines10112811.

171. Xu P, Sudarikova AV, Ilatovskaya DV et al. Epithelial Sodium Channel Alpha Subunit (αENaC) Is Associated with Inverse Salt Sensitivity of Blood Pressure. *Biomedicines.* 2022;10(5):981. doi: 10.3390/biomedicines10050981.

172.Li H, Shi S, Sun YH, et al. Dopamine D2 receptor stimulation inhibits angiotensin II-induced hypertrophy in cultured neonatal rat ventricular myocytes. *Clin Exp Pharmacol Physiol.* 2009;36(3):312-318.

doi: 10.1111/j.1440-1681.2008.05064.x.

173. Durdagi S, Erol I, Salmas RE, et al. Oligomerization and cooperativity in GPCRs from the perspective of the angiotensin AT1 and dopamine D2 receptors. *Neurosci Lett.* 2019;700:30-37. doi: 10.1016/j.neulet.2018.04.028

174. Wang X, Li F, Jose PA, et al. Reduction of renal dopamine receptor expression in obese Zucker rats: role of sex and angiotensin II. *Am J Physiol Renal Physiol.* 2010;299(5): F1164-1170. doi: 10.1152/ajprenal.00604.2009.

175. Hussain T, Abdul-Wahab R, Kotak DK, et al. Bromocriptine regulates angiotensin II response on sodium pump in proximal tubules. *Hypertension.* 1998;32(6):1054-1059. doi: 10.1161/01.hyp.32.6.1054.

176. Zhang MZ, Yao B, Fang X, et al. Intrarenal dopaminergic system regulates renin expression. *Hypertension.* 2009;53(3): 564-570.
doi:10.1161/HYPERTENSIONAHA.108.127035

177. Yang S, Yao B, Zhou Y, et al. Intrarenal dopamine modulates progressive angiotensin II-mediated renal injury. *Am J Physiol Renal Physiol.* 2012;302(6):F742-9.
doi: 10.1152/ajprenal.00583.2011.

178. Matsuyama T, Ohashi N, Ishigaki S, et al. The relationship between the intrarenal dopamine system and intrarenal renin-angiotensin system depending on the renal function. *Intern Med.* 2018;57(22):3241-3247. doi: 10.2169/internalmedicine.0994-18.

179. Drake CR Jr, Ragsdale NV, Kaiser DL, et al. Dopaminergic suppression of angiotensin II-induced aldosterone secretion in man: differential responses during sodium loading and depletion. *Metabolism.* 1984;33(8):696-702. doi: 10.1016/0026-0495(84)90207-5.

180. Barnett R, Singhal PC, Scharschmidt LA, et al. Dopamine attenuates the contractile response to angiotensin II in isolated rat glomeruli and cultured mesangial cells. *Circ Res* 1986;59(5):529-533.
doi: 10.1161/01.res.59.5.529

181. Kouyoumdzian NM, Rukavina Mikusic NL, et al. Acute infusion of angiotensin II regulates organic cation transporters function in the kidney: its impact on the renal dopaminergic system and sodium excretion. *Hypertens Res.* 2021;44(3):286-298. doi: 10.1038/s41440-020-00552-7.

182. Rukavina Mikusic NL, Kouyoumdzian NM, et al. Losartan prevents the imbalance between renal dopaminergic and renin angiotensin systems induced by fructose overload. l-Dopa/dopamine index as new potential biomarker of renal dysfunction. *Metabolism.* 2018;85:271-285.
doi: 10.1016/j.metabol.2018.04.010.

183. Yamaguchi I, Yao L, Sanada H, et al. Dopamine D1A receptors and renin release in rat juxtaglomerular cells. *Hypertension.* 1997;29(4):962-8.
doi: 10.1161/01.hyp.29.4.962.

184. Zeng C, Asico LD, Wang X, et al. Angiotensin II regulation of AT1 and D3 dopamine receptors in renal proximal tubule cells of SHR. *Hypertension.* 2003;41(3 Pt 2):724-9.
doi: 10.1161/01.HYP.0000047880.78462.0E..

185. Gross M-L P. Koch A, Mühlbauer B, et al. Renoprotective effect of a dopamine D3 receptor antagonist in experimental type II diabetes. *Lab Invest.* 2006;86(3):262-74. doi: 10.1038/labinvest.3700383.

186. Sanada H, Yao L, Jose PA, et al. Dopamine D3 receptors in rat juxtaglomerular

cells. *Clin Exp Hypertens.* 1997;19(1-2):93-105. doi: 10.3109/10641969709080807.

187.Luippold G, Max A, Albinus M, et al. Role of the renin-angiotensin system in the compensation of quinpirole-induced blood pressure decrease. Naunyn Schmiedebergs *Arch Pharmacol.* 200;367(5):427-33. doi: 10.1007/s00210-003-0740-5.

188. Chen K, Deng K, Wang X, et al. Activation of D4 Dopamine Receptor Decreases Angiotensin II Type 1 Receptor Expression in Rat Renal Proximal Tubule Cells. *Hypertension.* 2015;65(1):153-60.
doi: 10.1161/HYPERTENSIONAHA.114.04038.

189. Moore SC, Vaz de Castro PAS, Yaqub D, et al. Anti-Inflammatory Effects of Peripheral Dopamine. Int J Mol Sci. 2023;24(18):13816. doi: 10.3390/ijms241813816.

190. Rukavina Mikusic NL, Silva MG, Mazzitelli LR, et al. Interaction Between the Angiotensin-(1-7) Mas Receptor and the Dopamine D2 Receptor: Implications in Inflammation. Hypertension and Inflammation – *Hypertension.* 2021;77(5):1659-1669. doi: 10.1161/HYPERTENSIONAHA.120.16614.

191. Feng Y, Lu Y. Immunomodulatory Effects of Dopamine in Inflammatory Diseases. *Front Immunol.* 2021:12:663102.
doi: 10.3389/fimmu.2021.663102.

192. Yang J, Villar VAM, Jose PA, et al. Renal Dopamine Receptors and Oxidative Stress: Role in Hypertension. *Antioxid Redox Signal.* 2021;34(9):716-735.
doi: 10.1089/ars.2020.8106.

193. Banday AA, Lau YS, Lokhandwala MF. Oxidative stress causes renal dopamine D1 receptor dysfunction and salt-sensitive hypertension in Sprague-Dawley rats. *Hypertension.* 2008;51(2):367-75.
doi: 10.1161/HYPERTENSIONAHA.107.102111.

194. Xia XG, Schmidt N, Teismann P, et al. Dopamine mediates striatal malonate toxicity via dopamine transporter-dependent generation of reactive oxygen species and D2 but not D1 receptor activation. *J Neurochem.* 2001;79 (1):63-70.
doi: 10.1046/j.1471-4159.2001.00525.x.

195. Charvin D, Vanhoutte P, Pagès C, et al. Unraveling a role for dopamine in Huntington's disease: the dual role of reactive oxygen species and D2 receptor stimulation. *Proc Natl Acad Sci USA.* 2005;102(34):12218-12223. doi: 10.1073/pnas.0502698102.

196. Cosentino M, Rasini R, Colombo C, et al. Dopaminergic modulation of oxidative stress and apoptosis in human peripheral blood lymphocytes: evidence for a D1-like receptor-dependent protective effect. *Free Radic Biol Med.* 2004;36(10):1233-40.
doi: 10.1016/j.freeradbiomed.2004.02.065.

197. Acquier AB, Mori Sequeiros García M, Gorostizaga AB, et al. Reactive oxygen species mediate dopamine-induced signaling in renal proximal tubule cells. *FEBS Lett.* 2013;587(19):3254-60.
doi: 10.1016/j.febslet.2013.08.020.

198. Rosin C, Colombo S, Calver AA, et al. Dopamine D2 and D3 receptor agonists limit oligodendrocyte injury caused by glutamate oxidative stress and oxygen/glucose deprivation. *Glia.* 2005;52(4):336-43.
doi: 10.1002/glia.20250.

199. Odaka H, Numakawa T, Adachi N, et al. Cabergoline, dopamine D2 receptor agonist, prevents neuronal cell death under oxidative stress via reducing excitotoxicity. *PLoS One.* 2014;9(6):e99271.
doi: 10.1371/journal.pone.0099271.

200. Oster S, Radad K, Scheller D, et al. Rotigotine protects against glutamate toxicity in primary dopaminergic cell culture. *Eur J Pharmacol.* 2014:724:31-42. doi: 10.1016/j.ejphar.2013.12.014.

201. Niewiarowska-Sendo A, Kozik A, Guevara-Lora I. Influence of bradykinin B2 receptor and dopamine D2 receptor on the oxidative stress, inflammatory response, and apoptotic process in human endothelial cells. *PLoS One.* 2018 Nov 14;13(11):e0206443. doi: 10.1371/journal.pone.0206443.

202. Cuevas S, Yang Y, Konkalmatt P, et al. Role of nuclear factor erythroid 2-related factor 2 in the oxidative stress-dependent hypertension associated with the depletion of DJ-1. *Hypertension.* 2015;65(6):1251-1257. doi: 10.1161/HYPERTENSIONAHA.114.0452

203. Lieberknecht V, Junqueira SC, Cunha MP. et al. Pramipexole, a Dopamine D2/D3 Receptor-Preferring Agonist, Prevents Experimental Autoimmune Encephalomyelitis Development in Mice. *Mol Neurobiol.* 2017;54(2):1033-1045. doi: 10.1007/s12035-016-9717-5.

204. Shibagaki K, Okamoto K, Katsuta O, Nakamura M. Beneficial protective effect of pramipexole on light-induced retinal damage in mice. *Exp Eye Res.* 2015:139:64-72. doi: 10.1016/j.exer.2015.07.007.

205. Wang Z, Guan W, Han Y, et al. Stimulation of Dopamine D3 Receptor Attenuates Renal Ischemia-Reperfusion Injury via Increased Linkage With Gα12. *Transplantation.* 2015;99 (11):2274-84. doi: 10.1097/TP.0000000000000762.

206. Ferrari-Toninelli G, Maccarinelli G, Uberti D, Buerger E, Memo M. Mitochondria-targeted antioxidant effects of S(-) and R(+) pramipexole. *BMC Pharmacol.* 2010:10:2. doi: 10.1186/1471-2210-10-2.

207. Liu X, Guo Y, Yang Y, et al. DRD4 (DopamineD4Receptor) Mitigate Abdominal Aortic Aneurysm via Decreasing P38 MAPK (mitogen-activated protein kinase)/NOX4 (NADPH Oxidase 4) Axis-Associated Oxidative Stress. *Hypertension.* 2021;78(2):294-307. doi: 10.1161/HYPERTENSIONAHA.120.16738.

208. Shimada S, Hirabayashi M, Ishige K, et al. Activation of dopamine D4receptors is protective against hypoxia/reoxygenation-induced cell death in HT22 cells. *J Pharmacol Sci.* 2010;114(2):217-24. doi: 10.1254/jphs.10134fp.

209. Ishige K, Chen Q, Sagara Y, Schubert D. The activation of dopamine D4 receptors inhibits oxidative stress-induced nerve cell death. *J Neurosci.* 2001;21(16):6069-76. doi: 10.1523/JNEUROSCI.21-16-06069.2001.

210. Li XX, Bek M, Asico LD, et al. Adrenergic and endothelin B receptor-dependent hypertension in dopamine receptor type-2 knockout mice. *Hypertension.* 2001;38(3): 303-8. doi: 10.1161/01.hyp.38.3.303.

211. Martinez-Pinilla E, Rodriguez-Perez AI, Navarro G, et al. Dopamine D_2 and angiotensin II type 1 receptors form functional heteromers in rat striatum. *B Biochem Pharmacol.* 2015;96 (2):131-42. doi: 10.1016/j.bcp.2015.05.006.

212. Camargo LL, Wang Y, Rios FJ, McBride M, Montezano AC, Touyz RM. Oxidative Stress and Endoplasmic Reticular Stress Interplay in the Vasculopathy of Hypertension. *Can J Cardiol.* 2023;39(12):1874-1887. doi: 10.1016/j.cjca.2023.10.012.

213. Qaddumi WN, Jose PA. The Role of the Renal Dopaminergic System and Oxidative

Stress in the Pathogenesis of Hypertension. *Biomedicines.* 2021;9(2):139. doi:10.3390/biomedicines9020139.

214. Didik S, Wang H, James AS, Slotabec L, Li J. Sestrin2 as a Potential Target in Hypertension. *Diagnostics* (Basel). 2023;13 (14):2374. doi: 10.3390/diagnostics13142374.

215. Cowley AW Jr, Abe M, Mori T, et al. Reactive oxygen species as important determinants of medullary flow, sodium excretion, and hypertension. *Am J Physiol Renal Physiol.* 2015;308(3):F179-97. doi: 10.1152/ajprenal.00455.2014.

216. Cuevas S, Zhang Y, Yang Y, et al. Role of renal DJ-1 in the pathogenesis of hypertension associated with increased reactive oxygen species production. *Hypertension.* 2012;59(2): 446-52. doi: 10.1161/HYPERTENSIONAHA.111.185744.

217. Yang Y, Zhang Y, Cuevas S., et al. Paraoxonase 2 decreases renal reactive oxygen species production, lowers blood pressure, and mediates dopamine D2 receptor-induced inhibition of NADPH oxidase. *Free Radic Biol Med.* 2012;53(3):437-446. doi:10.1016/j.freeradbiomed.2012.05.015.

218. Yang Y, Cuevas S, Yang S, et al. Sestrin2 decreases renal oxidative stress, lowers blood pressure, and mediates dopamine D2 receptor-induced inhibition of reactive oxygen species production. *Hypertension.* 2014;64(4):825-32. doi: 10.1161/HYPERTENSIONAHA.114.03840.

219. Cuevas S, Villar VA, Jose PA, Armando I. Renal dopamine receptors, oxidative stress, and hypertension. *Int J Mol Sci.* 2013;14(9): 17553-72. doi: 10.3390/ijms140917553.

220. Lassègue B, San Martín A, Griendling KK. Biochemistry, physiology, and pathophysiology of NADPH oxidases in the cardiovascular system. *Circ Res.* 2012;110(10): 1364-90. doi: 10.1161/CIRCRESAHA.111.243972.

221. Touyz RM, Anagnostopoulou A, Camargo LL, Rios RJ, Montezano AC. Vascular Biology of Superoxide-Generating NADPH Oxidase 5-Implications in Hypertension and Cardiovascular Disease. *Antioxid Redox Signal.* 2019;30(7):1027-1040. doi: 10.1089/ars.2018.7583.

222. Yu P, Han W, Villar VAM et al. Unique role of NADPH oxidase 5 in oxidative stress in human renal proximal tubule cells. *Redox Biol.* 2014:2:570-9. doi: 10.1016/j.redox.2014.01.020.

223. Tanase DM, Apostol AG, Costea CF, et al. Oxidative Stress in Arterial Hypertension (HTN): The Nuclear Factor Erythroid Factor 2-Related Factor 2 (Nrf2) Pathway, Implications and Future Perspectives. *Pharmaceutics.* 2022; 14(3):534. doi: 10.3390/pharmaceutics14030534.

224. Bao B, Liu H, Han Y, Xu L, Xing W, Li Z. Simultaneous Elimination of Reactive Oxygen Species and Activation of Nrf2 by Ultrasmall Nanoparticles to Relieve Acute Kidney Injury. *ACS Appl Mater Interfaces.* 2023;15(13): 16460-16470. doi: 10.1021/acsami.3c00052.

225. Wan SR, Teng FY, Fan W, et al. BDH1-mediated βOHB metabolism ameliorates diabetic kidney disease by activation of NRF2-mediated antioxidative pathway. *Aging (Albany NY).* 2023;15(22):13384-13410. doi: 10.18632/aging.205248.

226. Mapuskar KA, Pulliam CF, Zepeda-Orozco D, et al. Redox Regulation of Nrf2 in Cisplatin-Induced Kidney Injury. *Antioxidants (Basel).* 2023;12(9):1728. doi: 10.3390/antiox12091728.

227. Wang C, Luo Z, Carter G. NRF2 prevents hypertension, increased ADMA, microvascular oxidative stress, and dysfunction in mice with two weeks of ANG II infusion. *Am J Physiol Regul Integr Comp Physiol.* 2018;314(3): R399-R406. doi: 10.1152/ajpregu.00122.2017.

228. Goldberg MS, Pisani A, Haburcak M, et al. Nigrostriatal dopaminergic deficits and hypokinesia caused by inactivation of the familial Parkinsonism-linked gene DJ-1. *Neuron.* 2005;45(4):489-96.
doi: 10.1016/j.neuron.2005.01.041.

229. Yin L, Li H, Liu Z, Wu W, Cai J, Tang C, Dong Z. PARK7 Protects Against Chronic Kidney Injury and Renal Fibrosis by Inducing SOD2 to Reduce Oxidative Stress. *Front Immunol.* 2021:12:690697.
doi: 10.3389/fimmu.2021.690697.

230. Cuevas S, Yang Y, Konkalmatt P, et al. Role of nuclear factor erythroid 2-related factor 2 in the oxidative stress-dependent hypertension associated with the depletion of DJ-1. *Hypertension.* 2015;65(6):1251-7. doi: 10.1161/HYPERTENSIONAHA.114.04525.

231. Carey RM, Thorner O, Ortt EM. Dopaminergic inhibition of metoclopramide-induced aldosterone secretion in man. Dissociation of responses to dopamine and bromocriptine. *J Clin Invest.* 1980;66(1):10-18. doi: 10.1172/JCI109822.

232. Chang H-W, Chu T-S, Huang H-W, et al. Down-regulation of D2 dopamine receptor and increased protein kinase Cmu phosphorylation in aldosterone-producing adenoma play roles in aldosterone overproduction. *J Clin Endocrinol Metab.* 2007;92(5):1863-70. doi: 10.1210/jc.2006-2338.

233. Miyata K, Rahman M, Shokoji T, et al. Aldosterone stimulates reactive oxygen species production through activation of NADPH oxidase in rat mesangial cells. *J Am Soc Nephrol.* 2005;16:2906–2912.
doi: 10.1681/ASN.2005040390.

234. Fernandes MH, Soares-da-Silva P. Role of monoamine oxidase and catechol-O-methyltransferase in the metabolism of renal dopamine. *J Neural Transm Suppl.* 1994:41: 101-5. doi: 10.1007/978-3-7091-9324-2_13.

235. De Marchi U, Mancon M, Battaglia V, Ceccon S, Cardellini P, Toninello A. Influence of reactive oxygen species production by monoamine oxidase activity on aluminum-induced mitochondrial permeability transition. *Cell Mol Life Sci.* 2004;61(19-20):2664-71. doi: 10.1007/s00018-004-4236-3.

236. Vindis C, Séguélas MH, Lanier S, Parini A, Cambon C. Dopamine induces ERK activation in renal epithelial cells through H2O2 produced by monoamine oxidase. *Kidney Int.* 2001;59(1):76-86.
doi: 10.1046/j.1523-1755.2001.00468.x.

237. Bianchi P, Séguélas M-H, Parini A, Cambon C. Activation of pro-apoptotic cascade by dopamine in renal epithelial cells is fully dependent on hydrogen peroxide generation by monoamine oxidases. *J Am Soc Nephrol.* 2003;14(4):855-862.
doi: 10.1097/01.asn.0000058909.00567.5c.

238. Seif-El-Nasr M, Atia AS, Abdelsalam RM. Effect of MAO-B inhibition against ischemia-induced oxidative stress in the rat brain. Comparison with a rational antioxidant. *Arzneimittelforschung.* 2008;58(4):160-7. doi: 10.1055/s-0031-1296487.

239. Zhang XR, Wang YX, Zhang ZJ, Li L, Reynolds GP. The effect of chronic antipsychotic drug on hypothalamic expression of neural nitric oxide synthase and dopamine D2

receptor in the male rat. *PLoS One.* 2012;7(4): e33247. doi: 10.1371/journal.pone.0033247.

240. Pyne-Geithman GJ, Caudell DN, Cooper M, Clark JF, Shutter LA. Dopamine D2-receptor-mediated increase in vascular and endothelial NOS activity ameliorates cerebral vasospasm after subarachnoid hemorrhage in vitro. *Neurocrit Care.* 2009;10(2):225-31. doi: 10.1007/s12028-008-9143-2.

241. Wilcox, C.S. Oxidative stress and nitric oxide deficiency in the kidney: A critical link to hypertension? *Am J Physiol Regul Integr Comp Physiol.* 2005;289(4):R913-35. doi: 10.1152/ajpregu.00250.2005.

242. Duan J, Wainwright MS, Comeron JM, et al. Synonymous mutations in the human dopamine receptor D2 (DRD2) affect mRNA stability and synthesis of the receptor. *Hum Mol Genet.* 2003;12(3):205-16. doi: 10.1093/hmg/ddg055.

243. Gholipour N, Ohradanova-Repic A, Ahangari G. A novel report of MiR-4301 induces cell apoptosis by negatively regulating DRD2 expression in human breast cancer cells. *J Cell Biochem.* 2018;119(8):6408-6417. doi: 10.1002/jcb.26577.

244. Bhatnagar P, Barron-Casella E, Bean CJ, et al. Genome-wide meta-analysis of systolic blood pressure in children with sickle cell disease. *PLoS One.* 2013;8(9):e74193. doi: 10.1371/journal.pone.007419.

245. Nguweneza A, Oosterwyk C, Banda K, et al. Factors associated with blood pressure variation in sickle cell disease patients: a systematic review and meta-analyses. *Expert Rev Hematol.* 2022;15(4):359-368. doi: 10.1080/17474086.2022.2043743.

246. Han F, Konkalmatt P, Chen J, et al. miR-217 mediates the protective effects of the dopamine D2 receptor on fibrosis in human renal proximal tubule cells. *Hypertension.* 2015; 65(5): 1118–1125. doi:10.1161/HYPERTENSIONAHA.114.05096

247. Xie J, Li S, Ma X, Li R, Zhang H, Li J, Yan X. MiR-217-5p inhibits smog (PM2.5)-induced inflammation and oxidative stress response of mouse lung tissues and macrophages through targeting STAT1. *Aging (Albany NY).* 2022; 14(16):6796-6808. doi: 10.18632/aging.20425.

248. Zhang H, Chen F, Liang Z, et al. Analysis of miRNAs and their target genes associated with mucosal damage caused by transport stress in the mallard duck intestine. *PLoS One.* 2020;15(8):e0237699. doi: 10.1371/journal.pone.0237699.

249. Shi L, Tian Z, Fu Q, Li H, Zhang L, Tian L, Mi W. miR-217-regulated MEF2D-HDAC5/ND6 signaling pathway participates in the oxidative stress and inflammatory response after cerebral ischemia. *Brain Res.* 2020:1739:146835. doi: 10.1016/j.brainres.2020.14683

250. Yan J, Yang F, Wang D, Lu Y, Liu L, Wang Z. MicroRNA-217 modulates inflammation, oxidative stress, and lung injury in septic mice via SIRT1. *Free Radic Res.* 2021;55(1):1-10. doi: 10.1080/10715762.2020.1852234.