

Review Article

Relationship between Apelin/APJ Signaling, Oxidative Stress, and Diseases

Shuangyu Lv ¹, Yu Feng,¹ Qiying Jiang,¹ Xinrui Lv ², and Yanjie Yang ¹

¹Institute of Molecular Medicine, School of Basic Medical Sciences, Henan University, Kaifeng 475004, China

²The Department of Physiology, School of Basic Medical Sciences, Henan University, Kaifeng 475004, China

Correspondence should be addressed to Xinrui Lv; lvxinrui@126.com and Yanjie Yang; yangyj@henu.edu.cn

Received 17 September 2020; Revised 23 December 2020; Accepted 15 January 2021; Published 27 January 2021

Academic Editor: Giuseppe Cirillo

Copyright © 2021 Shuangyu Lv et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Apelin, a peptide hormone, is an endogenous ligand for G protein-coupled receptor and has been shown to be widely expressed in human and animal tissues, such as the central nervous system and adipose tissue. Recent studies indicate that the apelin/APJ system is involved in the regulation of multiple physiological and pathological processes, and it is associated with cardiovascular diseases, metabolic disorders, neurological diseases, ischemia-reperfusion injury, aging, eclampsia, deafness, and tumors. The occurrence and development of these diseases are closely related to the local inflammatory response. Oxidative stress is that the balance between oxidation and antioxidant is broken, and reactive oxygen species are produced in large quantities, causing cell or molecular damage, which leads to vascular damage and a series of inflammatory reactions. Hence, this article reviewed recent advances in the relationship between apelin/APJ and oxidative stress, and inflammation-related diseases, and highlights them as potential therapeutic targets for oxidative stress-related inflammatory diseases.

1. Introduction

Apelin (APLN), a bioactive neuropeptide derived from 77 amino acids [1], is an endogenous ligand for APJ receptors (APLNR) [2], first acquired from bovine gastric tissue [3]. The prepeptide of APLN was cleaved and processed by protease to form various derived molecular forms, such as apelin-36, apelin-26, pyr-apelin-13, and apelin-12, and the most active form is apelin-13 [3]. Apelin is a novel adipocytokine [4] that acts on G protein-coupled receptors (APJ) through APJ signaling [5].

Receptor protein APJ is an intron-free gene in the coding region, mainly binding to apelin-13 specificity, and the sequence is similar to the angiotensin receptor type 1 (AT1) gene [2, 6]. APJ can be detected in a variety of organs and tissues other than APLN, including the brain, heart, skin, retinal endothelium, adipose tissue, blood vessels, and cardiovascular system [7]. As we all know, the apelin/APJ system plays a key physiological role in cardiovascular action, neovascularization [8], energy metabolism [9], glucose metabolism [10], and pain [11, 12] and is involved in cardio-

vascular disease, metabolic syndrome, and diabetes [13–15]. Evidence suggests that the antioxidant activity of APLN is significant in some areas.

Oxidative stress (OS) refers to a state in which in vivo oxidation is out of balance with antioxidant action, which tends to be oxidized, leading to neutrophil inflammatory infiltration and an increase of protease secretion, resulting in a large number of oxidative intermediates. OS occurs when free radicals produce more than the ability of the antioxidant protective system [16] and is considered to be an important factor leading to aging and disease. The prooxidants produce reactive oxygen species (ROS) during normal metabolism, such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), most of which are cleared by antioxidants such as superoxide dismutase (SOD), glutathione reductase, and vitamin E in vivo, and a small fraction of the ROS plays an important role in maintaining vascular tension and participating in membrane receptor-mediated signal transduction [17].

Increased ROS can lead to tissue and molecular damage, such as damage to proteins, lipids, amino acids, and nucleic

acids [18, 19], and even the DNA damage and apoptosis of cardiomyocytes [20, 21]. Therefore, high-efficiency antioxidants can be used to inhibit ROS accumulation and oxidative damage. The antioxidant enzymes neutralize highly reactive free radicals and thus prevent uncontrolled production of ROS [22]. A recent study demonstrates that APLN reduces the production and release of ROS in adipocytes by APJ receptors. This suggests APLN makes an important contribution to the reduction of OS in adipocytes and stress in other tissues stimulated by ROS [23].

A number of studies have shown that APLN have anti-inflammatory and antioxidant effects [23–26]. Therefore, we systematically summarize the relationship between apelin/APJ, OS, and inflammation-related diseases, as well as the related pathological processes involved in APLN. This article reviewed the recent advances in the role of the apelin/APJ system in related diseases caused by OS.

1.1. Apelin in Cardiovascular Disease. Apelin/APJ system plays an important role in the cardiovascular system, including enhancing myocardial contractility, lowering blood pressure, inhibiting cardiomyocyte hypertrophy, and reducing atherosclerosis. APLN can regulate blood pressure and angiogenesis through different mechanisms. APLN mitigates hypertension by modulating nitric oxide (NO) signaling pathways and renin-angiotensin-aldosterone system (RAAS). Vascular NO bioavailability and OS imbalance can cause hypertension and vascular injury [27, 28]. The application of intravenous injection to male Wistar rats with apelin-13 produced antihypertensive effect [29], which was mainly through the release of endothelial nitric-oxide synthase (eNOS) phosphorylation to promote endothelium-dependent vasodilation; thus, achieving the goal of lowering blood pressure [24]. Zhou et al. showed that apelin-12 exhibited the most significant antihypertensive effect after intraperitoneal injection of apelin-12, apelin-13, and apelin-36 in anesthetized rats [24]. Nevertheless, there was no significant change in blood pressure in APJ-deficient mice injected with APLN, suggesting that vasodilation function and lowering blood pressure can only be developed by binding to intact endothelial APJ. Altogether, APLN can inhibit oxidative stress associated with hypertension via the eNOS/NO pathway [24, 30].

Furthermore, APLN has also been shown to induce hypertension by oxidative stress. The renin-angiotensin system (RAS) main active metabolites Angiotensin (Ang) II commonly contribute to hypertension, vascular injury, and heart and kidney failure by activating AT1 receptor-mediated effects [31]. The angiotensin-converting enzyme 2 (ACE2)/Ang-(1-7)/Mas receptor axis has been shown to reduce hypertension and improve vascular damage by increasing NO bioavailability and reducing ROS production [32]. It was known that apelin-13 promotes an increase of NOX4 expression [33]. Nevertheless, under physiological and pathological conditions, apelin/APJ has a completely opposite effect on RAS function and antagonizes Ang II, suggesting that APLN can induce hypertension by regulating the NOX4-Ang II pathways [34, 35].

Apelin abrogates the development of atherosclerosis via increasing the NO bioavailability and inhibiting Ang II cellular signaling [36]. Nevertheless, Zhou et al. and Hashimoto et al. demonstrate that the apelin/APJ system promoted OS-induced atherosclerosis, which was mediated by the phosphatidylinositol 3-kinase (PI3K)/(protein kinase B) Akt/extracellular-regulated kinase 1/2 (ERK1/2) pathway and APLN-induced nuclear factor- κ B (NF- κ B)/c-Jun N-terminal kinase (JNK) expression, implying that the development of stable APJ receptor antagonists may provide new therapeutic tools for cardiovascular disease [24, 37]. It was reported that apelin could reduce OS induced by 5-hydroxytryptamine or hydrogen peroxide (H₂O₂) and protect mice from ventricular hypertrophy through a reduction in ROS generation [38]. Apelin-13 promoted the expression of cardiac myosin and β -MHC (β -myosin heavy chain) mRNA 15 days after chronic infusion into the paraventricular nucleus of normal blood pressure rats, indicating that apelin-13 could induce cardiac hypertrophy [39]. Moreover, endoplasmic reticulum stress leads to the dysregulation of intracellular Ca²⁺ and activation of calcineurin-nuclear factor of activated T cell 3 (NFAT3) signaling pathway, leading to cardiac hypertrophy. Ceylan-Isik et al. found that endoplasmic reticulum stress was significantly attenuated by the application of APLN [40]. Apelin-13 improved the cardiac dysfunction, impaired cardiac hemodynamics, and attenuated fibrosis of cardiac fibroblasts, which was presented as reducing the levels of collagen I, collagen III, α -smooth muscle actin (SMA), and transforming growth factor- β (TGF- β) induced by Ang II via inhibiting the PI3K/Akt signaling pathway to inhibit OS [41].

Moreover, APLN has been shown to alleviate cardiotoxicity. Zhang et al. reported that apelin-13 pretreatment effectively attenuated the cisplatin-induced ROS and superoxide anion generation, inhibited DNA damage, and suppressed the poly ADP-ribose polymerase (PARP) cleavage and caspases activation, and participated in the regulation of mitogen-activated protein kinase (MAPKs) and PI3K/Akt signaling pathways, thus significantly reducing cisplatin-induced cardiac toxicity in vivo [42].

The role of APLN in the regulation of OS-induced cardiovascular disease is inconsistent. It may be due to different inducements of OS injury, animal species, forms of apelin, animal models, etc. The main molecular mechanisms of apelin/APJ in regulating oxidative stress-induced cardiovascular system diseases are associated with NO, Ang II, and PI3K/Akt. Apelin/APJ has been extensively studied in animal models of OS injury-induced cardiovascular disease. However, further studies are needed in the different APLN subtypes and their associated functions or their antioxidant role in cardiovascular disease. Apelin/APJ systems can be developed as novel drugs to treat cardiovascular diseases.

1.2. Apelin in Metabolic Disorders. Apelin is adipokines with insulinomimetic activity that are produced and released by adipose tissue [43, 44]. APLN not only inhibited the production and release of ROS but also attenuates oxidative stress-induced cellular dysfunctions in adipocytes [23]. Recently, Aung et al. reported that APLN increased the AMPK, Akt,

and ERK1/2 activation (phosphorylation) in adipocytes in a dose-dependent manner and stimulated mitochondrial biogenesis [23]. Apelin had recently been shown to rescue defects in insulin resistance by regulating AMPK signals [45, 46]. Tissue inhibitor of metalloproteinases 3 (TIMP3) deficiency leads to OS response, sphingolipid pathway, and lipid metabolism disorder, and injection APLN restores lipid oxidative defects [47].

Improving diet and exercise to lose weight can reduce OS and increase NO production. Therefore, increasing the availability of NO after weight loss surgery was a beneficial effect of weight loss. Roux-en-Y gastric bypass in diet-induced obese rats improved the NO bioavailability resulting from higher endothelial Akt/NO synthase activation, reduced JNK phosphorylation, and reduced OS. Exogenous ghrelin might be a candidate for therapeutic treatment of diabetes. OS was the main cause of gastrointestinal damage, and diabetes was associated with an increased production of ROS [48, 49]. Ghrelin had antioxidant effects on systemic OS and showed gastroprotective effects [49]. Ghrelin supplementation might help prevent some complications in diabetic rats.

1.3. Apelin in Neurological Diseases. The distribution of apelin in the central nervous system (CNS) suggests that the expression levels of APLN in the CNS changes significantly with nervous system injury caused by various neurological diseases [50]. Studies had shown that apelin inhibited the activation of NF- κ B [51] and thus protected nerve cells. Recently, Xu et al. reported that exogenous apelin-13 binding to APJ improved the neurological functions and attenuated early brain injury after subarachnoid hemorrhage (SAH) by reducing ER stress-mediated OS and neuroinflammation, which was at least partly mediated by the AMPK/TXNIP/NLRP3 signaling pathway. Therefore, apelin-13/APJ system could be a promising therapeutic target in the treatment of SAH [52].

Parkinson's disease is a common human neurodegenerative disease consisting mainly of aberrant aggregation and posttranslationally modified α -synuclein, while OS has been shown to form nitrated α -synuclein that can lead to the progressive death of dopaminergic neurons [53, 54]. It was reported that apelin-36 produced a neuroprotective effect against Parkinson's disease caused by the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injury. Zhu et al. showed that the neuroprotective mechanism of apelin-36 against MPTP-induced neurotoxicity in mice might be related to decreasing the aggregation of nitrated α -synuclein and alleviating OS as well as promoting autophagy and inhibiting ASK1/JNK/caspase-3 apoptotic pathway [55]. Methamphetamine (METH) is a potent psychomotor stimulant with neurotoxicity, especially in dopaminergic neurons. Long-lasting exposure to METH increases the risk of Parkinson's disease. In METH-induced PC12 cells, apelin-13 could potentially alleviate METH-induced neurotoxicity via the reduction of oxidative damages, apoptotic, and autophagy cell death [56].

Apelin-13 has been reported to show neuroprotective effects on cortical neurons by modulating serum deprivation-(SD-) induced OS and apoptosis [57]. Moreover, APLN

inhibited the excitotoxicity mediated by *N*-methyl-D-aspartic acid (NMDA) receptor in the hippocampus of rats (O'Donnell et al., 2007). Apelin may be beneficial to inhibit Alzheimer's disease (AD) pathology by inhibiting the role of Ang II and regulating the PI3K/AKT/GSK-3 β signaling pathways to inhibit hyperphosphorylation [58]. The disruption of Ca²⁺ homeostasis may be involved in the pathology of neurodegenerative diseases. APLN shows an inhibitory effect on the development of neurodegenerative diseases by reducing the Ca²⁺ concentration caused by increased sarco(endo)plasmic reticulum Ca²⁺-ATPase (SERCA) activity, suggesting that APLN may be a potential target for the treatment of neurodegenerative diseases [58]. It was reported that epilepsy is associated with increased OS, which may increase susceptibility to attention deficit hyperactivity disorder (ADHD) [16].

1.4. Apelin in Ischemia-Reperfusion Injury. The key factor in cardiac ischemia-reperfusion (I/R) injury is mitochondria-derived OS. It was demonstrated that structural analogs of adipocyte-derived peptide apelin-12 have potential effects on mitochondrial ROS generation, cardiomyocyte apoptosis, and metabolic and functional recovery from myocardial I/R injury, attenuating excess mitochondrial ROS production in myocardial I/R injury and maintaining myocardial metabolic status [59].

Recent studies demonstrated that apelin-13 protected the brain from I/R injury by the activation of ERK1/2 and PI3K/Akt signaling pathways [60]. Moreover, apelin-13 was showed to protect the heart against I/R injury through the RISK-GSK-3 β -mPTP pathway [61]. Even apelin-13 may improve the survival rate of casual flaps to some extent [62]. Apelin/APJ signaling may protect vascular reduction and tissue damage by inhibiting OS, thereby inhibiting skin I/R injury-induced pressure ulcer (pU) formation, and exogenous applications of APLN or MM07 (APJ biased agonists) may have therapeutic potential against pU development [63]. These results suggest that apelin alleviated I/R injury by regulating OS and thus exerted myocardial protection.

1.5. Apelin in Aging, Apoptosis, and Autophagy. Recent studies indicated that apelin is associated with aging. APLN deficiency leads to multiple organ aging [64]. Apelin alleviates OS which contributes to the development of aging. Increasing evidence showed APLN was involved in the autophagy process, and activation of autophagy protects cells from apoptosis [65, 66], which contributed to antiaging and alleviated OS [67, 68].

Apelin increased the glycosaminoglycan (GAG) content of nucleus pulposus (NP) cells and mRNA/protein expressions of NP matrix macromolecules (collagen II and Aggrecan) and promoted autophagic flux (LC3II/I increased and p62 decreased) under OS [69]. More importantly, obesity, diabetes, and cardiovascular disease, discussed above, are closely related to aging. In addition, Ca²⁺ dysregulation is reported to be related to aging [70].

1.6. Apelin in Women's Diseases. The APLN receptor system is known to have potential therapeutic target in preeclampsia. Recently, Wang et al. reported that APLN treatment

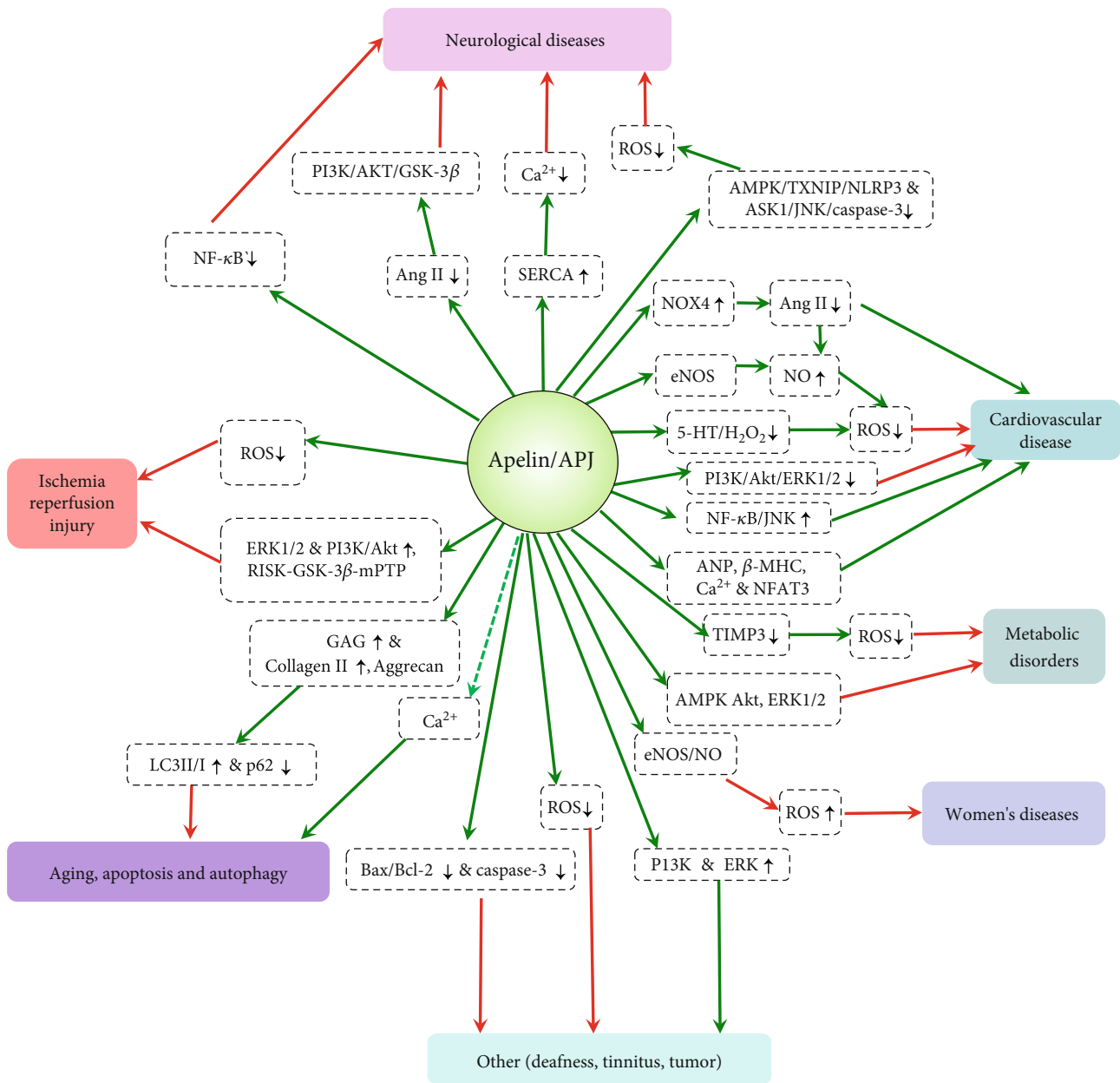


FIGURE 1: The association between apelin/APJ system and oxidative stress in various diseases.

significantly improved the symptoms of preeclampsia, mitigated impaired eNOS/NO signaling, and attenuated OS activation in uterine perfusion pressure (RUPP) rats [71]. In preeclampsia rat models, infusion of (Pyr)-apelin-13 not only reduced OS markers but also improved renal pathology, suggesting that (Pyr)-apelin-13 may have renal protection in preeclampsia [5]. At the same time, hemodynamic response and kidney injury could be improved after APLN treatment, and there was no fetal toxicity, indicating that APLN plays a role in regulating the prognosis of preeclampsia [5]. However, Incebiyik et al. had shown there were significantly higher APLN levels in premenstrual syndrome (PMS) patients than in healthy women [72].

1.7. Others. The apelin/APJ system plays a role in hearing loss. Pretreatment of hair cell-like cell-derived MSCS (as a model for OS-induced hearing loss) with apelin-13 could reduce the Bax/Bcl-2 ratio and caspase-3 protein expression and improve their survival under OS conditions [73] and protected against OS-induced hair cell damage. Apelin played a role in the pathophysiology of idiopathic tinnitus and may reduce OS in the future [72]. Kartal et al. found that apelin-13 could aggravate the decrease of erythrocyte deformability in rats with diabetes and IR injury [74].

With the continuous progress in relevant research, the roles of APLN and OS in tumors were emerged. Apelin has the effect of inhibiting the production of ROS, which indicated that APLN inhibited tumorigenesis by regulating OS.

However, Sorli et al. first reported that hypoxia induced by tumor cells could promote the expression level of APLN [75]. The increased ROS level induces hypoxia-inducible factor (HIF) expression in tumor stem cells (CSCs) in hypoxic environments [76]. Hence, it is speculated that ROS-induced OS is closely related to tumorigenesis and may be regulated by APLN. According to reports, APLN had been demonstrated to play a role in lymph node metastasis and lymphangiogenesis, activating ERK and PI3K pathways, leading to cell proliferation, migration, and cell survival [77].

2. Conclusion

In summary, the apelin/APJ system is closely related to OS, which can not only significantly reduce the production of ROS but also inhibit the oxidative stress response (Figure 1). In this review, we introduce APLN, outline the close correlation between APLN and OS, and discuss the underlying mechanisms by which apelin could improve OS injury in various ways. Therefore, recent reports reveal that APLN plays an important role in OS injury and can provide a reference direction for future research on the treatment of diseases in OS injury.

Data Availability

Data availability is not applicable because this is a review article.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Shuangyu Lv and Yu Feng wrote the draft of the manuscript. Yanjie Yang, Xinrui Lv, and Qiying Jiang contributed to the revision and writing of the manuscript. Shuangyu Lv and Yu Feng contributed equally to this work.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant No. 81971280 and No. 81600974), the Key Science and Technology Program of Henan Province (Grant No. 192102310151, No. 202102310213, and No. 192102310080), the Program for Young Key Teacher of Henan Province (Grant No. 2020GGJS037), the Youth Talent Promotion Plan of Henan Association for Science and Technology (Grant No. 2020HYTP054), the Natural Science Foundation for Excellent Young Scholars of Henan Province (Grant No. 212300410026), and the Research Program for Young Talent of Henan University School of Medicine (Grant No. 2019018).

References

- [1] D. K. Lee, R. Cheng, T. Nguyen et al., "Characterization of apelin, the ligand for the APJ receptor," *Journal of Neurochemistry*, vol. 74, no. 1, pp. 34–41, 2000.
- [2] B. F. O'Dowd, M. Heiber, A. Chan et al., "A human gene that shows identity with the gene encoding the angiotensin receptor is located on chromosome 11," *Gene*, vol. 136, no. 1-2, pp. 355–360, 1993.
- [3] K. Tatemoto, M. Hosoya, Y. Habata et al., "Isolation and characterization of a novel endogenous peptide ligand for the human APJ receptor," *Biochemical and Biophysical Research Communications*, vol. 251, no. 2, pp. 471–476, 1998.
- [4] F. Ferdinal, D. Limanan, R. D. Rini, R. Alessandro, and R. Helmi, "Elevated levels of apelin-36 in heart failure due to chronic systemic hypoxia," *International Journal of Angiology*, vol. 28, no. 3, pp. 194–199, 2019.
- [5] L. M. Yamaleyeva, K. B. Brosnihan, E. Elsangeedy et al., "Systemic outcomes of (pyr(1))-apelin-13 infusion at mid-late pregnancy in a rat model with preeclamptic features," *Scientific Reports*, vol. 9, no. 1, article 8579, 2019.
- [6] L. He, J. Xu, L. Chen, and L. Li, "Apelin/APJ signaling in hypoxia-related diseases," *Clinica Chimica Acta*, vol. 451, pp. 191–198, 2015.
- [7] A. Mughal and S. T. O'Rourke, "Vascular effects of apelin: mechanisms and therapeutic potential," *Pharmacology & Therapeutics*, vol. 190, pp. 139–147, 2018.
- [8] J. Pi, Y. Cheng, H. Sun et al., "Apln-CreERT:mT/mG reporter mice as a tool for sprouting angiogenesis study," *BMC Ophthalmology*, vol. 17, no. 1, p. 163, 2017.
- [9] N. A. Chapman, D. J. Dupre, and J. K. Rainey, "The apelin receptor: physiology, pathology, cell signalling, and ligand modulation of a peptide-activated class A GPCR," *Biochemistry and Cell Biology*, vol. 92, no. 6, pp. 431–440, 2014.
- [10] F. Kazemi and S. Zahediasl, "Effects of exercise training on adipose tissue apelin expression in streptozotocin-nicotinamide induced diabetic rats," *Gene*, vol. 662, pp. 97–102, 2018.
- [11] S. Lv, X. Zhang, Y. Zhou, Y. Feng, Y. Yang, and X. Wang, "Intrathecal administered apelin-13 alleviated complete Freund's adjuvant-induced inflammatory pain in mice," *Frontiers in Pharmacology*, vol. 11, article 1335, 2020.
- [12] S. Lv, X. Zhang, Y. Feng et al., "Intravenous administration of pyroglutamyl apelin-13 alleviates murine inflammatory pain via the kappa opioid receptor," *Frontiers in Neuroscience*, vol. 14, p. 929, 2020.
- [13] M. B. Wysocka, K. Pietraszek-Gremplewicz, and D. Nowak, "The role of apelin in cardiovascular diseases, obesity and cancer," *Frontiers in Physiology*, vol. 9, p. 557, 2018.
- [14] O. M. Leung, J. Li, X. Li et al., "Regulatory T cells promote apelin-mediated sprouting angiogenesis in type 2 diabetes," *Cell Reports*, vol. 24, no. 6, pp. 1610–1626, 2018.
- [15] M. Li, H. Fang, and J. Hu, "Apelin-13 ameliorates metabolic and cardiovascular disorders in a rat model of type 2 diabetes with a high-fat diet," *Molecular Medicine Reports*, vol. 18, no. 6, pp. 5784–5790, 2018.
- [16] M. Elhady, E. R. Youness, R. S. I. Mostafa, A. Abdel Aziz, and R. Hussein, "Oxidative stress contribution to attention deficit hyperactivity disorder in children with epilepsy," *Applied Neuropsychology: Child*, vol. 8, no. 4, pp. 347–354, 2019.
- [17] J. Masoumi, M. Abbasloui, R. Parvan et al., "Apelin, a promising target for Alzheimer disease prevention and treatment," *Neuropeptides*, vol. 70, pp. 76–86, 2018.
- [18] Y. Z. Fang, S. Yang, and G. Wu, "Free radicals, antioxidants, and nutrition," *Nutrition*, vol. 18, no. 10, pp. 872–879, 2002.

- [19] B. Halliwell, "Reactive oxygen species and the central nervous system," *Journal of Neurochemistry*, vol. 59, no. 5, pp. 1609–1623, 1992.
- [20] E. S. E. el-Awady, Y. M. Moustafa, D. M. Abo-Elmatty, and A. Radwan, "Cisplatin-induced cardiotoxicity: mechanisms and cardioprotective strategies," *European Journal of Pharmacology*, vol. 650, no. 1, pp. 335–341, 2011.
- [21] P. Ferroni, D. Della-Morte, R. Palmirotta et al., "Platinum-based compounds and risk for cardiovascular toxicity in the elderly: role of the antioxidants in chemoprevention," *Rejuvenation Research*, vol. 14, no. 3, pp. 293–308, 2011.
- [22] J. M. Matés, "Effects of antioxidant enzymes in the molecular control of reactive oxygen species toxicology," *Toxicology*, vol. 153, no. 1-3, pp. 83–104, 2000.
- [23] A. Than, X. Zhang, M. K.-S. Leow, C. L. Poh, S. K. Chong, and P. Chen, "Apelin Attenuates Oxidative Stress in Human Adipocytes," *Journal of Biological Chemistry*, vol. 289, no. 6, pp. 3763–3774, 2014.
- [24] Q. Zhou, J. Cao, and L. Chen, "Apelin/APJ system: a novel therapeutic target for oxidative stress-related inflammatory diseases (review)," *International Journal of Molecular Medicine*, vol. 37, no. 5, pp. 1159–1169, 2016.
- [25] B. Bircan, M. Çakır, S. Kırbag, and H. F. Gül, "Effect of apelin hormone on renal ischemia/reperfusion induced oxidative damage in rats," *Renal Failure*, vol. 38, no. 7, pp. 1122–1128, 2016.
- [26] I. Gunes, H. Kartal, A. D. Dursun et al., "Effects of apelin-13 on myocardial ischemia reperfusion injury in streptozotocine induced diabetic rats," *Bratislava Medical Journal*, vol. 119, no. 6, pp. 348–354, 2018.
- [27] M. G. Risbano and M. T. Gladwin, "Therapeutics targeting of dysregulated redox equilibrium and endothelial dysfunction," in *Pharmacotherapy of Pulmonary Hypertension*, M. Humbert, O. V. Evgenov, and J. P. Stasch, Eds., pp. 315–349, 2013.
- [28] N. Sinha and P. Dabla, "Oxidative stress and antioxidants in hypertension—a current review," *Current Hypertension Reviews*, vol. 11, no. 2, pp. 132–142, 2015.
- [29] D. K. Lee, V. R. Saldivia, T. Nguyen, R. Cheng, S. R. George, and B. F. O'Dowd, "Modification of the terminal residue of apelin-13 antagonizes its hypotensive action," *Endocrinology*, vol. 146, no. 1, pp. 231–236, 2005.
- [30] J. Ishida, T. Hashimoto, Y. Hashimoto et al., "Regulatory roles for APJ, a seven-transmembrane receptor related to angiotensin-type 1 receptor in blood pressure in vivo," *Journal of Biological Chemistry*, vol. 279, no. 25, pp. 26274–26279, 2004.
- [31] S. D. Crowley, S. B. Gurley, M. J. Herrera et al., "Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 103, no. 47, pp. 17985–17990, 2006.
- [32] G. Yang, P.-L. Chu, L. C. Rump, T. H. le, and J. Stegbauer, "ACE2 and the homolog collectrin in the modulation of nitric oxide and oxidative stress in blood pressure homeostasis and vascular injury," *Antioxidants & Redox Signaling*, vol. 26, no. 12, pp. 645–659, 2017.
- [33] L. Li, F. Li, F. Li et al., "NOX4-derived reactive oxygen species drive apelin-13-induced vascular smooth muscle cell proliferation via the ERK pathway," *International Journal of Peptide Research and Therapeutics*, vol. 17, no. 4, pp. 307–315, 2011.
- [34] K. Siddiquee, J. Hampton, S. Khan et al., "Apelin protects against angiotensin II-induced cardiovascular fibrosis and decreases plasminogen activator inhibitor type-1 production," *Journal of Hypertension*, vol. 29, no. 4, pp. 724–731, 2011.
- [35] X. Sun, S. Iida, A. Yoshikawa et al., "Non-activated APJ suppresses the angiotensin II type 1 receptor, whereas apelin-activated APJ acts conversely," *Hypertension Research*, vol. 34, no. 6, pp. 701–706, 2011.
- [36] H. J. Chun, Z. A. Ali, Y. Kojima et al., "Apelin signaling antagonizes Ang II effects in mouse models of atherosclerosis," *Journal of Clinical Investigation*, vol. 118, no. 10, pp. 3343–3354, 2008.
- [37] T. Hashimoto, M. Kihara, N. Imai et al., "Requirement of apelin-apelin receptor system for oxidative stress-linked atherosclerosis," *American Journal of Pathology*, vol. 171, no. 5, pp. 1705–1712, 2007.
- [38] C. Foussal, O. Lairez, D. Calise et al., "Activation of catalase by apelin prevents oxidative stress-linked cardiac hypertrophy," *FEBS Letters*, vol. 584, no. 11, pp. 2363–2370, 2010.
- [39] F. Zhang, H. J. Sun, X. Q. Xiong et al., "Apelin-13 and APJ in paraventricular nucleus contribute to hypertension via sympathetic activation and vasopressin release in spontaneously hypertensive rats," *Acta Physiologica*, vol. 212, no. 1, pp. 17–27, 2014.
- [40] A. F. Ceylan-Isik, M. R. Kandadi, X. Xu et al., "Apelin administration ameliorates high fat diet-induced cardiac hypertrophy and contractile dysfunction," *Journal Of Molecular and Cellular Cardiology*, vol. 63, pp. 4–13, 2013.
- [41] S. Zhong, H. Guo, H. Wang et al., "Apelin-13 alleviated cardiac fibrosis via inhibiting the PI3K/Akt pathway to attenuate oxidative stress in rats with myocardial infarction-induced heart failure," *Bioscience Reports*, vol. 40, no. 4, 2020.
- [42] P. Zhang, L.-h. Yi, G.-y. Meng, H. Y. Zhang, H. H. Sun, and L. Q. Cui, "Apelin-13 attenuates cisplatin-induced cardiotoxicity through inhibition of ROS-mediated DNA damage and regulation of MAPKs and AKT pathways," *Free Radical Research*, vol. 51, no. 5, pp. 449–459, 2017.
- [43] M. Olszanecka-Glinianowicz, P. Kocelak, M. Nylec, J. Chudek, and B. Zahorska-Markiewicz, "Circulating visfatin level and visfatin/insulin ratio in obese women with metabolic syndrome," *Archives of Medical Science*, vol. 2, no. 2, pp. 214–218, 2012.
- [44] J. Krist, K. Wieder, N. Klötting et al., "Effects of weight loss and exercise on apelin serum concentrations and adipose tissue expression in human obesity," *Obesity Facts*, vol. 6, no. 1, pp. 57–69, 2013.
- [45] C. Attane, C. Foussal, S. le Gonidec et al., "Apelin treatment increases complete fatty acid oxidation, mitochondrial oxidative capacity, and biogenesis in muscle of insulin-resistant mice," *Diabetes*, vol. 61, no. 2, pp. 310–320, 2012.
- [46] I. Castan-Laurell, C. Dray, C. Knauf, O. Kunduzova, and P. Valet, "Apelin, a promising target for type 2 diabetes treatment?," *Trends in Endocrinology and Metabolism*, vol. 23, no. 5, pp. 234–241, 2012.
- [47] R. Stöhr, B. A. Kappel, D. Carnevale et al., "TIMP3 interplays with apelin to regulate cardiovascular metabolism in hypercholesterolemic mice," *Molecular Metabolism*, vol. 4, no. 10, pp. 741–752, 2015.
- [48] V. M. Bhor, N. Raghuram, and S. Sivakami, "Oxidative damage and altered antioxidant enzyme activities in the small intestine of streptozotocin-induced diabetic rats,"

- International Journal of Biochemistry & Cell Biology*, vol. 36, no. 1, pp. 89–97, 2004.
- [49] H. Suzuki, J. Matsuzaki, and T. Hibi, “Ghrelin and oxidative stress in gastrointestinal tract,” *Journal of Clinical Biochemistry and Nutrition*, vol. 48, no. 2, pp. 122–125, 2011.
- [50] S.-Y. Lv, W.-D. Chen, and Y.-D. Wang, “The apelin/APJ system in psychosis and neuropathy,” *Frontiers in Pharmacology*, vol. 11, p. 320, 2020.
- [51] R. T. Day, R. C. Cavaglieri, and D. Feliers, “Apelin retards the progression of diabetic nephropathy,” *American Journal of Physiology-Renal Physiology*, vol. 304, no. 6, pp. F788–F800, 2013.
- [52] W. Xu, T. Li, L. Gao et al., “Apelin-13/APJ system attenuates early brain injury via suppression of endoplasmic reticulum stress-associated TXNIP/NLRP3 inflammasome activation and oxidative stress in a AMPK-dependent manner after subarachnoid hemorrhage in rats,” *Journal of Neuroinflammation*, vol. 16, no. 1, p. 247, 2019.
- [53] E. J. Benner, R. Banerjee, A. D. Reynolds et al., “Nitrated alpha-synuclein immunity accelerates degeneration of nigral dopaminergic neurons,” *Plos One*, vol. 3, no. 1, article e1376, 2008.
- [54] R. Dringen, “Oxidative and antioxidative potential of brain microglial cells,” *Antioxidants & Redox Signaling*, vol. 7, no. 9–10, pp. 1223–1233, 2005.
- [55] J. Zhu, W. Gao, X. Shan et al., “Apelin-36 mediates neuroprotective effects by regulating oxidative stress, autophagy and apoptosis in MPTP-induced Parkinson's disease model mice,” *Brain Research*, vol. 1726, article 146493, 2020.
- [56] K. Foroughi, M. Khaksari, M. Rahmati, F. S. Bitaraf, and A. Shayannia, “Apelin-13 protects PC12 cells against methamphetamine-induced oxidative stress, autophagy and apoptosis,” *Neurochemical Research*, vol. 44, no. 9, pp. 2103–2112, 2019.
- [57] X. J. Zeng, S. P. Yu, L. Zhang, and L. Wei, “Neuroprotective effect of the endogenous neural peptide apelin in cultured mouse cortical neurons,” *Experimental Cell Research*, vol. 316, no. 11, pp. 1773–1783, 2010.
- [58] H. Luo, L. Han, and J. Xu, “Apelin/APJ system: a novel promising target for neurodegenerative diseases,” *Journal of Cellular Physiology*, vol. 235, no. 2, pp. 638–657, 2019.
- [59] O. Pisarenko, V. Shulzhenko, I. Studneva et al., “Structural apelin analogues: mitochondrial ROS inhibition and cardiometabolic protection in myocardial ischaemia reperfusion injury,” *British Journal of Pharmacology*, vol. 172, no. 12, pp. 2933–2945, 2015.
- [60] Y. Yang, X. Zhang, H. Cui, C. Zhang, C. Zhu, and L. Li, “Apelin-13 protects the brain against ischemia/reperfusion injury through activating PI3K/Akt and ERK1/2 signaling pathways,” *Neuroscience Letters*, vol. 568, pp. 44–49, 2014.
- [61] S. Yang, H. Li, L. Tang et al., “Apelin-13 protects the heart against ischemia-reperfusion injury through the RISK-GSK-3 β -mPTP pathway,” *Archives of Medical Science*, vol. 11, no. 5, pp. 1065–1073, 2015.
- [62] W. Zheng, J. Wang, L. Xie et al., “An injectable thermosensitive hydrogel for sustained release of apelin-13 to enhance flap survival in rat random skin flap,” *Journal of Materials Science-Materials in Medicine*, vol. 30, no. 9, p. 106, 2019.
- [63] S. Yamazaki, A. Sekiguchi, A. Uchiyama et al., “Apelin/APJ signaling suppresses the pressure ulcer formation in cutaneous ischemia-reperfusion injury mouse model,” *Scientific Reports*, vol. 10, no. 1, p. 1349, 2020.
- [64] R. Rai, A. K. Ghosh, M. Eren et al., “Downregulation of the apelinergic axis accelerates aging, whereas its systemic restoration improves the mammalian healthspan,” *Cell Reports*, vol. 21, no. 6, pp. 1471–1480, 2017.
- [65] W. Jiang, X. Zhang, J. Hao et al., “SIRT1 protects against apoptosis by promoting autophagy in degenerative human disc nucleus pulposus cells,” *Scientific Reports*, vol. 4, no. 1, article 7456, 2015.
- [66] S. Miyazaki, K. Kakutani, T. Yurube et al., “Recombinant human SIRT1 protects against nutrient deprivation-induced mitochondrial apoptosis through autophagy induction in human intervertebral disc nucleus pulposus cells,” *Arthritis Research & Therapy*, vol. 17, no. 1, p. 253, 2015.
- [67] F. Yao, Y.-C. Lv, M. Zhang et al., “Apelin-13 impedes foam cell formation by activating class III PI3K/Beclin-1-mediated autophagic pathway,” *Biochemical and Biophysical Research Communications*, vol. 466, no. 4, pp. 637–643, 2015.
- [68] D. Liang, D. Han, W. Fan et al., “Therapeutic efficacy of apelin on transplanted mesenchymal stem cells in hindlimb ischemic mice via regulation of autophagy,” *Scientific Reports*, vol. 6, no. 1, article 21914, 2016.
- [69] W. Jiang, P. Zhao, and X. Zhang, “Apelin promotes ECM synthesis by enhancing autophagy flux via TFEB in human degenerative NP cells under oxidative stress,” *Biomed Research International*, vol. 2020, Article ID 4897170, 8 pages, 2020.
- [70] A. Kumar, K. Bodhinathan, and T. C. Foster, “Susceptibility to calcium dysregulation during brain aging,” *Frontiers in Aging Neuroscience*, vol. 1, p. 2, 2009.
- [71] C. Wang, X. Liu, D. Kong et al., “Apelin as a novel drug for treating preeclampsia,” *Experimental and Therapeutic Medicine*, vol. 14, no. 6, pp. 5917–5923, 2017.
- [72] A. Incebiyik, A. Camuzcuoglu, N. G. Hilali et al., “Serum oxidative stress, visfatin and apelin in healthy women and those with premenstrual syndrome,” *Journal of Obstetrics and Gynaecology*, vol. 35, no. 2, pp. 188–192, 2014.
- [73] S. Niknazar, H.-A. Abbaszadeh, H. Peyvandi et al., “Protective effect of [Pyr1]-apelin-13 on oxidative stress-induced apoptosis in hair cell-like cells derived from bone marrow mesenchymal stem cells,” *European Journal of Pharmacology*, vol. 853, pp. 25–32, 2019.
- [74] H. Kartal, F. M. Comu, A. Kucuk, Y. Polat, A. D. Dursun, and M. Arslan, “Effect of apelin-13 on erythrocyte deformability during ischaemia-reperfusion injury of heart in diabetic rats,” *Bratislava Medical Journal*, vol. 118, no. 3, pp. 133–136, 2017.
- [75] S. C. Sorli, S. le Gonidec, B. Knibiehler, and Y. Audigier, “Apelin is a potent activator of tumour neoangiogenesis,” *Oncogene*, vol. 26, no. 55, pp. 7692–7699, 2007.
- [76] J. Liu and Z. Wang, “Increased oxidative stress as a selective anticancer therapy,” *Oxidative Medicine and Cellular Longevity*, vol. 2015, Article ID 294303, 12 pages, 2015.
- [77] A. Booth, A. Magnuson, J. Fouts, and M. Foster, “Adipose tissue, obesity and adipokines: role in cancer promotion,” *Hormone Molecular Biology and Clinical Investigation*, vol. 21, no. 1, pp. 57–74, 2015.