UCH-L1: Implications in the Developmental Onset of PD and Hypertension

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Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCH-L1), a key player in the Ubiquitin-Proteasome System (UPS) and protein degradation, is spotlighted in this review for its involvement in Parkinson's Disease (PD) and hypertension. UCH-L1 has been found to mitigate the development of PD by reducing the formation of protein aggregates (Lewy bodies) within the substantia nigra of the brain. Hypertension induces the upregulation of UCH-L1, which activates various signaling pathways leading to cardiac remodeling in hypertensive rat models. Inhibitors targeting UCH-L1, such as LDN-57444, have demonstrated potential in attenuating hypertension. However, these inhibitors also pose a risk of neurotoxicity by impeding protein degradation. Therefore, a delicate balance in UCH-L1 modulation is crucial to ensure therapeutic benefits for potential human patients without causing adverse effects. This review accentuates the necessity for comprehensive research to thoroughly understand UCH-L1's mechanisms in hopes of developing safer, more specific treatments for future patients.

Keywords: Behavioral and Social Sciences; Neuroscience, UCH-L1, Hypertension, Parkinson's Disease Cellular and molecular biology; Cell Physiology; Neurobiology

Introduction

Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCH-L1) is a deubiquitinating enzyme that is part of the Ubiquitin-Proteasome System (UPS)[1,2]. It has several functions including ligase and hydrolase activities. UCH-L1 works to hydrolyze peptide ubiquitin bonds, recycles the ubiquitin monomers for the same process, and additionally, its ligase activity has been shown to promote α-synuclein aggregation in vitro[3]. It has a major role in the UPS, performing ubiquitin-dependent proteolysis by converting polymeric ubiquitin to monomeric ubiquitin[4]. In this process, ubiquitin is activated and polymerized to dysfunctional or damaged proteins for proteasomal degradation[5]. The UCH-L1 gene encodes a protein that makes up 1-2% of total soluble brain protein, and thus the expression of this gene is highly present throughout the brain[1,6].

UCH-L1 is made up of one domain, the C-12 peptidase domain[7]. Its function is to balance substrate entry into the catalytic site[8]. In this domain, there are about 6 types of sites, which are cysteine sites, N-myristoylation sites, Casein Kinase II Phosphorylation sites, Protein kinase C phosphorylation sites[9], and unconventional pathway secretion sites[10]. There is also one site outside of the C-12 peptidase domain, the farnesylation site[11], located at the C-terminal[7] (Figure 1). From these domains and sites, most harmful UCH-L1 mutations accumulate on the C-12 peptidase domain, though the majorly researched S18Y polymorphism has been shown to have a protective function in UCH-L1 against the development of neurological diseases like PD[12].

Hypertension is defined as an increase in blood pressure characterized by systolic blood pressure (SBP) values over 130 mm Hg or diastolic blood pressure values over 80 mm Hg. Additionally, it has been associated with PD symptoms[13]. Hypertension is a very common chronic condition delineated by constantly elevated arterial pressure, and generally increases risk of cardiac, cerebral, and renal complications[14], as well as multiple disorders like PD. Furthermore, in relation to PD, hypertension has been displayed to be a risk factor for motor stage PD[15].

As much past research has suggested, there have been clues that mutations in UCH-L1 lead to the development of neurological diseases like PD[16–20]. One mutation that will be presented in this paper is the I93M mutation, as well as the S18Y polymorphism. So far, the I93M mutation has only been shown in a single case of a German family affected by PD and therefore has been made uncertain whether the mutation is pathogenic or not[16,21,22]. On the other hand, the S18Y polymorphism has been shown to have a more controversial link to PD, not yet clearly being shown to provide any risk for PD development[23]. Therefore, this paper will seek to understand more about these mutations to find any possible correlations with PD development, as well as UCH-L1's influence in the symptom onset of PD and hypertension.

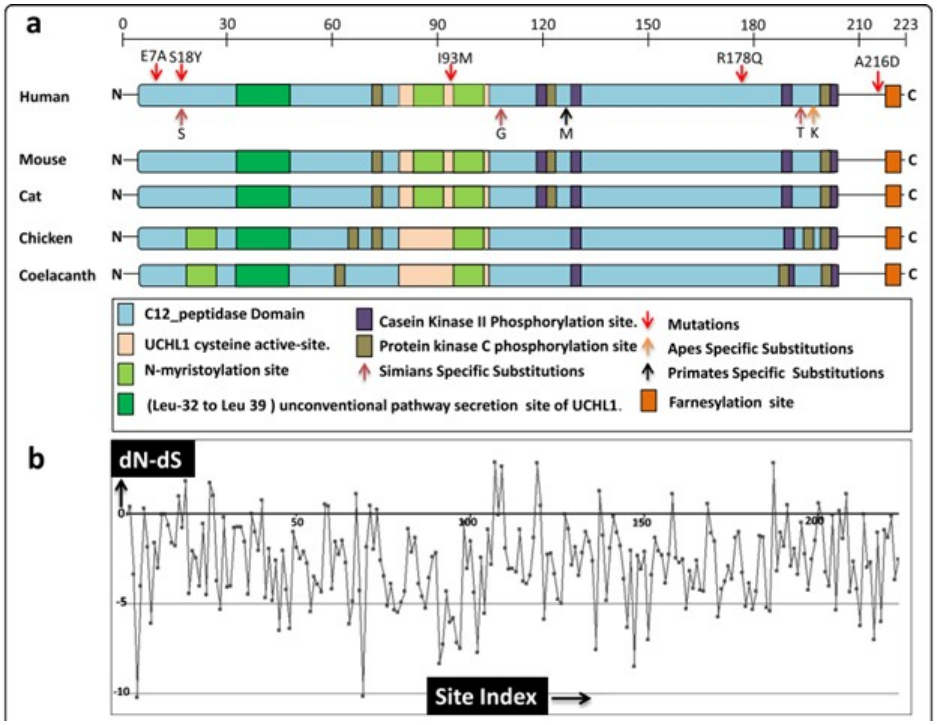

Fig. 1 Domains organization of UCH-L1 protein. a Diagrammatic representation of UCH-L1 domains and motifs. Schematic view of comparative organization of domains and motifs of UCH-L1 orthologous proteins from phylogenetically distant species. Protein and domain lengths are drawn approximately to scale. Domains and motifs are color-coded. Numbers on the scale represent amino acids. b Plot depicts those amino acid sites of UCH-L1 that are under negative selection constraint in sarcopterygians. X-axis depicts the site index of each residue of UCH-L1 and the y-axis depicts the dN-dS rate analysis of each amino acid residue of UCH-L1 (Reprinted from Nawaz et al, 2020[7])

Methodology

To conduct this literature review, several methods were used to ensure quality in my article. For source identification, databases including Google Scholar, PubMed, and ScienceDirect were used. For example, the use of Google Scholar's search engine allowed me to find more relevant and specific sources to solidify the evidential basis of my research based on my search terms, such as Parkinson's Disease and UCH-L1. Furthermore, apart from using search engines, I also utilized the Snowball method, where I located sources for my paper from the reference lists of relevant sources.

The keyword descriptors I selected for my literary analysis consisted of: Behavioral and Social Sciences, Neuroscience, UCH-L1, Hypertension, Parkinson's Disease, Cellular and molecular biology, Cell Physiology, Neurobiology, Translational medical sciences, Disease Prevention, Disease Treatment and Therapies, Drug Identification and Testing. All of these terms were chosen on the basis of their relatedness to the aim of the review.

To specifically decide if a source was a good fit as evidence to use in the review, I heavily relied on the abstract and conclusion of the articles to efficiently evaluate them for their applicability to my research for possible usage. In addition, I also evaluated the sources based on the following criteria: (1) Does the source align with my research topic? (2) How recent is the publication date of the sources? (3) Are the sources and credentials of their authors credible? I intended to solely utilize sources published within the last two decades, although a minority of sources preceded this timeline to lay the groundwork for concepts that remain applicable today.

Role of UCH-L1 in the Ubiquitin-Proteasome System

The UPS plays a crucial role in neurons, by regulating the removal of abnormal and dysfunctional proteins[24–26]. Without this constant regulation by the UPS, the buildup of dead proteins may be toxic, thus destroying the neuron[27]. Therefore, the ubiquitin-proteasome pathway must always function normally, to keep the neuron alive. As this system functions, the protein ubiquitin binds to proteins ready for degradation by an isopeptide linkage, specifically to the ε-amino group of lysine in the protein-bound for degradation[26]. Then, this linkage connects the carboxy terminus of the ubiquitin molecule to the lysine ε-amino group of another ubiquitin protein, to form polyubiquitin

chains[28]. Three main categories of enzymes help to run to the UPS, which are ubiquitin-activation enzymes (E1), ubiquitin transport enzymes (E2), and ligases (E3)[29,30]. Throughout the process, E1, the activation enzyme, works to move ubiquitin to the E2 enzyme, to finally be bound to the dysfunctional protein with assistance from the E3 ligases[26].

The I93M mutation is caused by a substitution of isoleucine for methionine at position 93[31]. In mice species, overexpression of α-synuclein has led to a decrease in dopaminergic cells in I93M transgenic mice[32], compared to little effects in UCH-L1 wild-type mice, proposing that the I93M mutation may cause a malignant function in UCH-L1[17]. Recent studies done by Yasuda et al.[33], Setsuie and Wada[18], Setsuie et al.[34], Kabuta et al.[35,36], and Kabuta and Wada[37], have shown that the I93M mutation exerts its effects through an increase in toxic function instead of a decrease in its hydrolytic function in vitro. In addition, the mutant (I93M) has been displayed to be less stable than the wild-type and unfolds around 10 times faster than the wild type, complementary to the fact that many of I93M's exchange rates are much quicker than that of the wild type, and have a crystal structure very similar to the wild type (both having comparable α-helices 5 and 6 and Met82 and Lys83)[17]. Therefore, this indicates that the destabilization effect of I93M alone could be the main cause of neurodegeneration caused by the mutation.

The Mechanism of UCH-L1 Influence on the Developmental Onset of PD

PD can be associated with UCH-L1 as Lewy bodies, or irregular protein aggregations containing α-synuclein, may be incorrectly removed, thus leading to its buildup in the UPS. The expression of the I93M mutation has been shown to increase levels of α-synuclein, which inhibits UPS function and has been associated with the developmental onset of PD and neurotoxicity[38]. Excess of this protein is further displayed to hinder the clearance of misfolded proteins, leading to their buildup[39,40]. As a deubiquitinating enzyme, UCH-L1 plays the role of degrading defective proteins like α-synuclein, along with hydrolyzing ubiquitin from poly-ubiquitin chains and ligating ubiquitin onto other proteins[41]. Additionally, UCH-L1 binds onto mono-Ub, helping to balance levels of ubiquitin in the protein[39].

The onset of PD symptoms has been observed to be caused by misfolding or improper degradation of proteins[42,43]. Two major factors can be seen to lead to the developmental onset of PD: the pathogenic protein α-synuclein and oxidative stress[44]. The protein α-synuclein has been shown to form aggregates or clumps in the brain, in vitro[40,45]. The process of α-synuclein aggregation is characterized by a slow lag phase followed by a rapid phase where larger clumps are formed. This process can be further sped up by environmental neurotoxicants like pesticides and herbicides, therefore creating more clumps at a faster rate, and contributing to the onset of PD symptoms[46].

How misfolding of the α-synuclein protein occurs is still largely a mystery, but it is known that three systems, the UPS, macroautophagy, and CMAP all function to remove α-synuclein protein[43,46]. From a study done by Cartier et al., UCH-L1 was tested in rat models to observe its impact on α-syn expression[47]. Data collected in this study showed that the inhibition of UCH-L1 activity in α-syn-overexpressed neurons reduced levels of expression of the α-syn protein, along with its distribution. It was shown that blockage of UCH-L1 activity in untreated mice (absence of UCH-L1 inhibitor) increased α-syn levels while limiting UCH-L1 activity in transgenic mice decreased α-syn levels. These changes in α-syn expression were further observed to be linked with unregulated autophagy in α-syn transgenic mice. Even with this evidence, the specific mechanisms by which UCH-L1 alters α-syn expression are still largely unclear and will need further research to validate.

The α-syn protein is also known to be removed by macroautophagy, a cleansing process for cells. In this process, organelles and misfolded substrates are segregated into double-membrane autophagosomes, which then fuse with lysosomes for digestion. Specific adaptors like p62 aid the transportation of misfolded proteins to the autophagosomes. However, mutations in the p62 gene are linked to neurological diseases like Paget Disease and ALS[43,48], suggesting that impaired removal of misfolded substrates can lead to neurodegenerative diseases like PD.

In addition, CMAP is a process that seeks to remove toxic or harmful proteins from the cell and works with the UPS. CMAP only targets proteins expressing KFERQ, a degradation signal that is found only in about 30% of cellular proteins. Many of these proteins carrying this signal are typical of neurodegenerative diseases like PD, Alzheimer's Disease (AD), and Huntington's Disease (HD)[44]. Thus, as the process involves the recognition of irregular folds in proteins and works with cochaperones to unfold the proteins, CMAP is a crucial system in helping to unfold misfolded proteins along with working with the other two systems to remove target proteins.

The S18Y polymorphism is a DNA sequence with a single nucleotide variation that occurs when serine is substituted with tyrosine at codon 18 in exon 3 of UCH-L1[49,50]. Through past studies, this polymorphism has not had a strong correlation with PD but is generally associated with age at PD onset, usually among younger people[23]. Several studies have illustrated that this polymorphism has shown to have protective effects in the UCH-L1 gene against PD[51,52]. In one study done by Xilouri et al., it was concluded that overexpression of S18Y UCH-L1 in the nigral region led to protection against MPTP, a chemical known to be toxic to neurons[53,54], therefore backing up evidence that this polymorphism has neuroprotective effects and is a potent antioxidant[51]. In addition to this study, another

study has observed that the S18Y polymorphism's antioxidant ability protects neuronal cells against oxidative stress, which is suspected of playing a role in different forms of sporadic PD[52].

As illustrated, several mutations on the UCH-L1 gene have been seen on the gene's single domain and have been linked to neurological diseases like PD, such as E7A, I93M, R178Q, and A216D mutations[7]. Only the I93M and S18Y variants have been extensively researched so far, with I93M being implicated in PD onset, while S18Y has been seen to have neuroprotective effects against PD[17,52]. While there are still uncertainties about both having links to neurological diseases, especially S18Y, this polymorphism has been shown to encode a protein that favors the degradation of the α-synuclein protein, therefore implying that it may be a protective factor in PD.

As mentioned, the major S18Y and I93M variants not only have links to onset PD development but also significantly affect this gene's functions in the UPS. Past studies have shown that the S18Y polymorphism increases hydrolase activity in UCH-L1, decreases E3 activity, and has neuroprotective effects through its antioxidant function. On the other hand, the I93M mutation drastically decreases hydrolase activity and also lowers E3 function[17,23,25]. In addition, in the case of a deletion of an active site residue, the result might be oxidative damage to the brain, which could alter the gene's function and allow it to interact with molecules like Lamp2a, thus stopping chaperone-mediated autophagy (CMAP) and increasing the buildup of proteins like α-synuclein.

UCH-L1's Impact on Blood Pressure Regulation and its Potential Role in Hypertension Etiology? It has previously been shown that UCH-L1 plays a role as a deubiquitinating enzyme (DUB) for hypertensive cardiac remodeling in rat models[55]. Data from this study revealed that blockage of UCH-L1 activity causes a decrease in hypertension, attenuating the effects of oxidative stress, inflammation, fibrosis, and cardiac hypertrophy. It was also demonstrated that UCH-L1 expression was significantly increased in spontaneously hypertensive rats both at the protein levels and at mRNA, which suggests that higher levels of UCH-L1 expression could potentially regulate cardiac remodeling[55]. To add on, increased expression of this gene can largely determine the pathogenesis of hypertensive retinopathy, and restriction of its expression slows down disease progression, suggesting that UCH-L1 is a possible therapeutic target to treat hypertension[56].

UCH-L1 has been seen to regulate the PI3K/AKT pathway as well by facilitating the degradation of p110a (PIK3CA), an isoform of the catalytic subunit of Class IA PI3K. UCH-L1 promotes this degradation of p110a through autophagy, but also interestingly increases AKT activity, promoting the polarization of macrophages into pro-inflammatory states[57] (Figure 2). Strengthening the past evidence that UCH-L1 leads to AKT activation through the upregulation of phosphorylated AKT[58–62], research by Huang et al. solidified those results by demonstrating that the deficiency of UCH-L1 leads to a decrease in the phosphorylation level of AKT in macrophages. In addition, as UCH-L1 is a deubiquitinase, it has been shown in past research to enhance the AKT pathway by reducing PHLPP1, which is a counteracting phosphatase. It has also been indicated to interact with the AKT by promoting K48 and K63 ubiquitination[61,63], and, as mentioned earlier, boosts AKT phosphorylation by encouraging p110a degradation through autophagy[57]. As the up-regulated PI3K/AKT signaling pathway has been found to contribute to sympathetic overdrive and hypertension, blocking this pathway effectively improves hypertension[64].

Past research has indicated that endoplasmic reticulum stress (ERS) is a key factor in the development of hypertensive vascular diseases. ERS, provoked by protein misfolding and buildup in the ER, triggers the unfolded protein response (UPR), which acts to improve the cell's ability to combat rising levels of ERS and reestablish ER homeostasis. However, the UPR can also become maladaptive, resulting in the release of inflammatory cytokines, which further increases ER stress by overpowering the folding capacity of the ER. This feedback loop is crucial in the development of pulmonary arterial hypertension (PAH), marked by vasoconstriction and vascular remodeling of the pulmonary artery[65]. Treatments like omentin-1 have exhibited potential in treating PAH by reducing ER stress via AMPKα signaling, although additional research is needed to explore the specific mechanisms by which omentin-1 regulates ER stress[66]. Suppressing ER stress has displayed potential to reduce heart damage and enhance vascular function, emphasizing its vital role in hypertension.

UCH-L1 has been displayed to lower AKT1 degradation, leading to elevated levels of AKT1. Since AKT1 is pathological in pulmonary hypertension, it was hypothesized that deficiency of UCH-L1 mitigates the development of PAH, by reducing AKT1 levels. Thus, this highlights a new potential therapeutic pathway for treating PAH.

Shared role of UCH-L1 in the Symptom Onset of PD and Hypertension

With hypertension's association as a risk factor for motor stage PD, additional studies have discovered other connections between the two disorders. Parkinson's patients were evaluated in a study by Tulba et al, under 24-hour ambulatory blood pressure monitoring[67]. Blood pressure fluctuations were observed throughout the day in these PD patients. From the data collected, the majority of the patients were found to have abnormal blood pressure, with 38.13% having hypertension, 38.68% having orthostatic hypotension, 38.91% having nocturnal hypertension, and 27.76% having supine hypertension. Autonomic dysfunction was the concluded

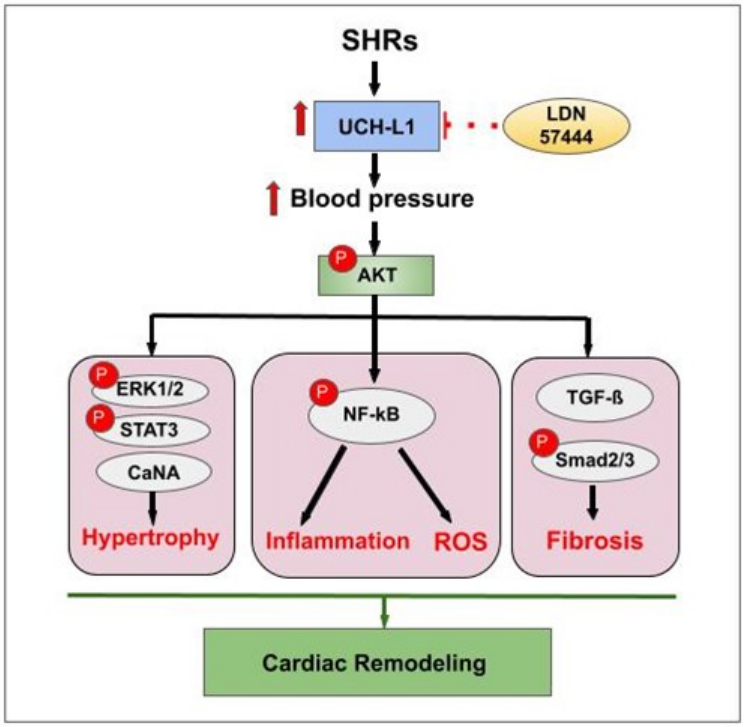

Fig. 2 A working model for LDN-57444 to attenuate cardiac remodeling in SHRs. Hypertension induces UCH-L1 upregulation, which activates multiple signaling pathways and induces hypertrophy, inflammation, oxidative stress, and fibrosis, thereby leading to cardiac remodeling in hypertensive rats. Conversely, blocking UCH-L1 activity by LDN-57444 protects against these effects (Reprinted from Han et al, 2020[55]).

explanation for these alterations, defined as a loss of control over bodily processes that are not conscious, like blood pressure, bladder, and bowel movements. These may be caused by residual sympathetic activity and changes in the sensitivity in vascular adrenergic receptors[67].

Thus, it is suggested that people who are predisposed to PD have a more likely chance of also experiencing cardiac disease symptoms and hypertension. It is also possible that reduced cognitive functioning was linked with PD diagnosis, along with carrying more cardiovascular risk factors. This further presents the idea that PD patients with these risk factors are more likely to be cognitively impaired compared to patients without cardiovascular risk factors[68]. Another study introduced the PD treatment Levodopa, which for some experiments had protective effects in hypotension and reduced vascular risk factors due to decreased autonomic activity with the progression of the disease[69,70]. On the contrary, other studies revealed that PD patients with vascular risk factors present led to other symptoms of PD, including motor movement difficulties[71]. Therefore, while it is still unclear how PD is linked with cardiovascular symptoms, it is now known that vascular risk factors can affect cognitive functioning and other factors in PD.

Much future research is needed to solidify this evidence and confirm that vascular risk factors in PD play a role in the development of cognitive impairment. Although past research has been able to solidify the linkage between the UCH-L1 gene with both PD and hypertension, little research or evidence has been found to suggest any correlation between PD and cardiovascular symptom onset.

Potential Inhibitors of UCH-L1 as Therapeutic Targets for UCH-L1-Related Pathologies

Several UCH-L1 inhibitors have been used in the past, including IMP-1710 (alkyne ABP), IMP-1711 (control compound), and LDN-57444, which has been the most tested inhibitor in UCH-L1 research. In past experiments, LDN has been used as a UCH-L1 inhibitor mainly in rat models but has led to some key findings[55,56]. The inhibitor targets UCH-L1 hydrolase activity and has been observed to attenuate hypertension in spontaneously hypertensive rats, leading to enhanced cardiac function, remodeling, decreased inflammation, and less oxidative stress compared with other treatments or methods[55].

LDN-57444, along with its linkage to hypertension, can also be seen to play a role in PD, as usage of this inhibitor to block UCH-L1 activity also downregulates monomeric ubiquitin, which largely decreases activity of the UPS and causes neuronal death[72]. This being said, the UPS system

plays a crucial role in PD as Lewy bodies, which are abnormal protein clusters containing α-synuclein, can accumulate if the UPS system malfunctions. α-synuclein interferes with UPS function, and excess of this protein can lead to a PD-linked mutation[39]. In this context, UCH-L1 serves as a deubiquitinating enzyme responsible for breaking down harmful proteins like α-synuclein. Therefore, the side effects of LDN-57444 blocking UCH-L1 and UPS activity can be fatal and possibly cause the onset of PD symptoms due to protein accumulation.

Discussion

In consideration of PD and hypertension, it has been proposed that hypertension may lead to the onset of motor PD through the increased likelihood of impaired cognition from cardiovascular risk factors, but extensive research is still needed to validify this association. As potential therapeutic targets of UCH-L1, inhibitors, most notedly LDN-57444, have been recently observed to reduce hypertension in spontaneously hypertensive rats (SHR), while also playing a pivotal role in PD to downregulate monomeric ubiquitin, which impairs UPS activity and therefore destroys the neuron.

UCH-L1's linkage with PD and hypertension has been substantiated through its involvement in the UPS pathway and ventricular modeling. As a therapeutic target to attenuate symptoms of both PD and hypertension, UCH-L1 inhibitors like LDN should continue to be tested to reinforce the correlation between PD and cardiac disease onset, to propose novel treatment strategies and confirm the existing evidence presented in this paper.

Due to the nature of this literature review, several limitations were faced when conducting the research, including the consideration that many gaps in the current knowledge of PD-hypertension correlation still exist, in which insufficient analysis of the known evidence is realistically quite plausible. In addition, given that this review was not a systematic review, not all papers on the given topic were addressed, and thus the review's purpose is to provide a summarized overview of the topic while suggesting new perspectives in future research.

Although it was concluded that PD and cardiac symptoms are associated, it can be noted that insufficient research has been performed to integrate existing studies on PD and hypertension. Therefore, future research should primarily focus on studying both diseases as an interconnected entity rather than considering each disease as independent. By fostering a comprehensive approach, it will be much easier to gain insight into the relationship between PD and hypertension to develop new therapeutic interventions for treating PD.

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