Brain Organoid and Systems Neuroscience Journal 2 (2024) 94–105

Contents lists available at ScienceDirect

Brain Organoid and Systems Neuroscience Journal

journal homepage: www.sciencedirect.com/journal/bosn

Review articles

# From peripheral to central (Neuro)degeneration: Is heart-kidney a new axial paradigm for Parkinson's disease?

Catarina Teixeira [a,b], Joana Martins-Macedo [a,c,d], Eduardo Gomes [e], Carla Soares-Guedes [a,e], Rita Caridade-Silva [a], Bruna Araújo [a,c,d], Cristiana Vilela [e], Inês Falcão Pires [b], Inês Alencastre [a], Fábio G. Teixeira [a,*]

[a] *i3S - Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal*
[b] *FMUP – Faculty of Medicine of University of Porto, Porto, Portugal*
[c] *Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal*
[d] *ICVS/3B's Associate Lab, PT Government Associated Lab, Braga, Guimarães, Portugal*
[e] *Center for Translational Health and Medical Biotechnology Research (TBIO)/Health Research Network(RISEHealth), ESS, Polytechnic of Porto, R. Dr. António Bernardino de Almeida, 400, Porto 4200-072, Portugal*

ARTICLE INFO

*Keywords:*
Parkinson's disease
Cardiovascular diseases
Chronic kidney disease
Brain-heart-kidney axis

ABSTRACT

Parkinson's Disease (PD) is primarily characterized by the accumulation of alpha-synuclein (αSyn) and the loss of dopaminergic neurons (DAn). The most evident repercussions of the disease include sympathetic and parasympathetic dysfunction, decreased dopamine (DA) levels, and impaired voluntary movements. Given the multifactorial nature of PD, it is now recognized that several systemic diseases may predispose individuals to the onset and progression of PD as well as influence its therapeutic outcomes. Recent studies have highlighted that patients with cardiovascular disease (CVD) and chronic kidney disease (CKD) face an increased risk of developing PD, independent of the shared risk factors. Indeed, substantial evidence supports the connections between the brain, heart, and kidneys. Elements such as the dopaminergic system, blood pressure regulation, inflammation, autophagy, oxidative stress, and calcium ($Ca^{2+}$) signaling are recognized as crucial for the functioning of each organ individually. However, these factors may also significantly impact the overall health of the triad. Understanding the interconnection between the brain, heart, and kidneys would be groundbreaking in enhancing our knowledge about their interactions, enabling prompt interventions in the early stages of the disease. With this perspective, this review analyzes the current understanding of the brain-heart-kidney axis as a potential new paradigm for diagnosing and managing PD.

## 1. Introduction

Parkinson's Disease (PD) is currently defined as a multifactorial neurodegenerative disorder affecting around 10 million people worldwide. Pathologically, PD is characterized by several key features, including the progressive loss of dopaminergic neurons (DAn) and alpha-synuclein (αSyn) deposition (Scorza et al., 2018; Jain and Goldstein, 2012; Cuenca-Bermejo et al., 2021; Acharya et al., 2020; Sharabi et al., 2021; Ma et al., 2019). Besides the brain, αSyn accumulation can also occur in various peripheral organs, such as the gut, pancreas, heart, and olfactory mucosa (Jain and Goldstein, 2012; Acharya et al., 2020; Hong et al., 2019; Oka et al., 2010; Titova et al., 2017). In 2003, Braak and colleagues proposed a model regarding the spread of αSyn, assuming that it can accumulate and form Lewy Bodies (LB) in specific gastrointestinal tract neurons (Braak et al., 2003a, 2003b). In line with this, many authors have posteriorly suggested that this spreading may extend to the CNS via the vagus nerve (Braak et al., 2003a, 2003b; Wakabayashi, 2020). As such, Braak's theory highlights a significant connection between the degeneration of the nigrostriatal system and parasympathetic nervous activity, given that the vagus nerve is primarily responsible for the parasympathetic innervation of nearly all organs (Sharabi et al., 2021; Braak et al., 2003b; Wakabayashi, 2020; Kitagawa et al., 2021). Nevertheless, the potential link between peripheral injury and the development and progression of PD is not entirely a new idea. Epidemiologic studies reveal that certain chronic diseases, such as diabetes mellitus, hypertension, and depression, are

* Correspondence to: Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto 4200-135, Portugal.
*E-mail address:* fteixeira@i3s.up.pt (F.G. Teixeira).

https://doi.org/10.1016/j.bosn.2024.11.003
Received 9 September 2024; Received in revised form 21 November 2024; Accepted 22 November 2024
Available online 26 November 2024

linked to an increased risk of developing neurodegenerative disorders, including PD (Nam et al., 2019). Additionally, patients with PD often exhibit dysfunction of the autonomic nervous system (ANS), and structural, functional, and molecular changes in the sympathetic nervous system (SNS) and parasympathetic nervous system (PSNS), which generally work to maintain homeostasis and facilitate the communication between the CNS and peripheral tissues (Jain and Goldstein, 2012; Cuenca-Bermejo et al., 2021; Titova et al., 2017). Given the heterogeneous etiology of PD, different manifestations between patients, and involvement of multiple systems, several authors have argued for classifying PD as a syndrome rather than a singular disease (Titova et al., 2017). This perspective arises from the understanding that PD is not solely characterized by physical motor symptoms leading to movement impairments, but also includes cognitive and non-cognitive non-motor symptoms (Titova et al., 2017).

In addition to this multifactorial level, recent studies have shown that beyond common risk factors such as diabetes mellitus and hypertension, patients with chronic kidney disease (CKD) and cardiovascular disease (CVD) have increased risk of PD, and blood pressure (BP) stands at the crossroads of this relationship (Acharya et al., 2020; Meléndez--Flores and Estrada-Bellmann, 2021; Ronco et al., 2008, 2018; Rangaswami et al., 2019; Pliquett, 2022; Uduman, 2018; Minciunescu et al., 2022; Quiroga et al., 2023; Junho et al., 2022; Gallo et al., 2023). Concerning the numbers, it is estimated that CKD accounts for approximately 1.2 million deaths globally, while CVDs are responsible for 17.7 million deaths. Additionally, around 1.4 million deaths are attributed to complications involving both cardiac and renal health (Meléndez-Flores and Estrada-Bellmann, 2021; Perrone and Valente, 2021). Indeed, Sstudies indicate that the chronic, systemic, and inflammatory conditions underlying CKD serve as significant triggers for processes that lead to vascular and myocardial remodeling, contributing to the development of atherosclerotic lesions, vascular calcification, and senescence, myocardial fibrosis, and calcification of cardiac valves (Baek et al., 2021; Alves et al., 2020). Consequently, a strong association has been established between CKD and increased risk of CVD – nearly 50% of deaths among CKD patients are due to cardiac events (Jankowski et al., 2021). Therefore, the simultaneous dysfunction of both the heart and kidneys is a common issue, and a disorder in one organ often leads to dysfunction in the other (Ronco et al., 2008). Such a relationship has led to the development of a new nomenclature: cardiorenal syndrome (CRS) (Ronco et al., 2008, 2018; Rangaswami et al., 2019; Pliquett, 2022; Uduman, 2018; Minciunescu et al., 2022; Quiroga et al., 2023; Junho et al., 2022; Gallo et al., 2023). In 2008, Ronco and colleagues classified CRS into five subtypes (types 1, 2, 3, 4, and 5) based on which organ is primarily affected and the duration of the dysfunction (Ronco et al., 2008). Despite the well-established classification of CRS, the cellular and molecular mechanisms underlying each subtype and the relationship between the heart and the kidneys remain largely unexplored.

Altogether, CKD and CVDs, along with PD, are among the leading causes of morbidity and mortality worldwide (Rai et al., 2023). Additionally, the interactions among the brain, heart, and kidneys –collectively named the brain-heart-kidney axis – are also poorly understood, especially regarding their interplay in disease states. In the present review, we aim to discuss the current understanding of PD, CKD, and CVD, addressing recent experimental data, exploring the brain-heart-kidney axis hypothesis, and examining potential mechanisms, signaling pathways, and key players involved in both normal and pathological conditions.

## 2. Parkinson's disease (PD)

PD is mainly characterized by the loss of DAn, in the nigrostriatal pathway (Scorza et al., 2018; Jain and Goldstein, 2012; Cuenca-Bermejo et al., 2021; Acharya et al., 2020; Sharabi et al., 2021; Ma et al., 2019; Kalia and Lang, 2015; Bloem et al., 2021). From the clinical set-point, such loss results in decreased dopamine (DA) levels, leading to motor impairment symptoms such as bradykinesia, resting tremors, muscular rigidity, and postural imbalance (Jain and Goldstein, 2012; Acharya et al., 2020; Hong et al., 2019; Oka et al., 2010; Kalia and Lang, 2015; Bloem et al., 2021; Reich and Savitt, 2019). Under physiological situations, αSyn binds to tyrosine hydroxylase (TH), inhibiting its activity and regulating DA synthesis. In PD, αSyn loses this function due to the aggregation into fibrils, leading to a loss of regulation over DA synthesis (Fig. 1) (Venda et al., 2010). This results in uncontrolled and toxic DA production while inhibiting the DA uptake by vesicular monoamine transporter (VMAT) (Fig. 1). Moreover, αSyn accumulation occurs not only in the brain but also in the spinal cord, vagus nerve, sympathetic ganglia, cardiac plexus, salivary glands, sciatic nerve, and other peripheral locations (Kalia and Lang, 2015). Additionally, protein accumulations, such as β-amyloid and tau, which are commonly associated with other neurodegenerative diseases such as Alzheimer's Disease, are also found in PD (Kalia and Lang, 2015). While these common features characterize PD, not all patients exhibit the same symptoms, complicating their diagnosis. Nowadays, non-motor symptoms are significant features of PD and often appear before primary motor symptoms. These non-motor symptoms include depression, dementia, rapid eye movement, sleep behavior disorder, constipation, orthostatic hypotension, postprandial hypotension, pain, and fatigue (Cuenca-Bermejo et al., 2021; Hong et al., 2019; Oka et al., 2010; Titova et al., 2017; Kalia and Lang, 2015; Bloem et al., 2021; Reich and Savitt, 2019). Despite their importance, the impact of non-motor dysregulations on the quality of life of PD patients is often underestimated, revealing new perspectives on this devastating disease.

Although the exact mechanism that triggers PD remains unclear, several factors are believed to increase an individual's likelihood of developing the pathology (see Table 1) (Kalia and Lang, 2015; Bloem et al., 2021). Well-established risk factors for PD include gender, ethnicity, and primarily age, and with the rise in life expectancy, it is estimated that the incidence of PD will increase by about 50% over the next 10 years (Kalia and Lang, 2015; Bloem et al., 2021). Additionally, environmental factors, such as the use of pesticides and prior head injuries, are also recognized as triggers for PD (Table 1) (Kalia and Lang, 2015; Bloem et al., 2021).

Genetics also plays a significant role in the onset of PD (Fig. 1). For autosomal dominant forms of PD, mutations in the SNCA and LRRK2 genes are among the most well-documented (Fig. 1). SNCA encodes the αSyn protein, and rare mutations in this gene are linked to the familial form of PD (Bloem et al., 2021). In contrast, LRRK2 encodes the leucine-rich repeat kinase 2, a GTPase and serine-threonine kinase that plays a role in neurite outgrowth, modulation of dopaminergic and glutamatergic synapses, membrane exchanges, autophagy, and protein synthesis (Bloem et al., 2021). This gene's mutation is the most common cause of genetically induced PD onset (Kalia and Lang, 2015; Bloem et al., 2021; Kim et al., 2019). Furthermore, a mutation in LRRK2 leads to the overactivation of BAX, a pro-apoptotic protein, releaseing cytochrome c, thereby increasing oxidative stress and apoptosis (Fig. 1). On the other hand, autosomal recessive forms of PD are characterized by an earlier onset of the disease and involve mutations in PARK2, PINK1, and DJ-1 genes (Fig. 1). Among these, PARK2, which encodes Parkin protein, is the most frequent cause of recessive onset (Kalia and Lang, 2015; Bloem et al., 2021). Mutations in these genes disrupt the regulation of proteins involved in mitochondrial metabolism, mitophagy, and apoptosis (Kalia and Lang, 2015; Bloem et al., 2021; Kim et al., 2019). For instance, a mutation in PINK1 inhibits the mitochondrial complex I, which leads to a deficient electron transport chain (Vizziello et al., 2021). Additionally, loss of function in the PINK1 gene results in Parkin's inactivation which is crucial for inhibiting apoptotic proteins (Fig. 1) (Vizziello et al., 2021). This mechanism is similar to the one associated with the loss of function of the DJ-1 protein (Fig. 1). In addition to their roles in mitophagy, PINK1 and Parkin have separate pro-survival mechanisms that help prevent neuronal cell death. Consequently, mutations in the genes encoding these proteins are linked to the

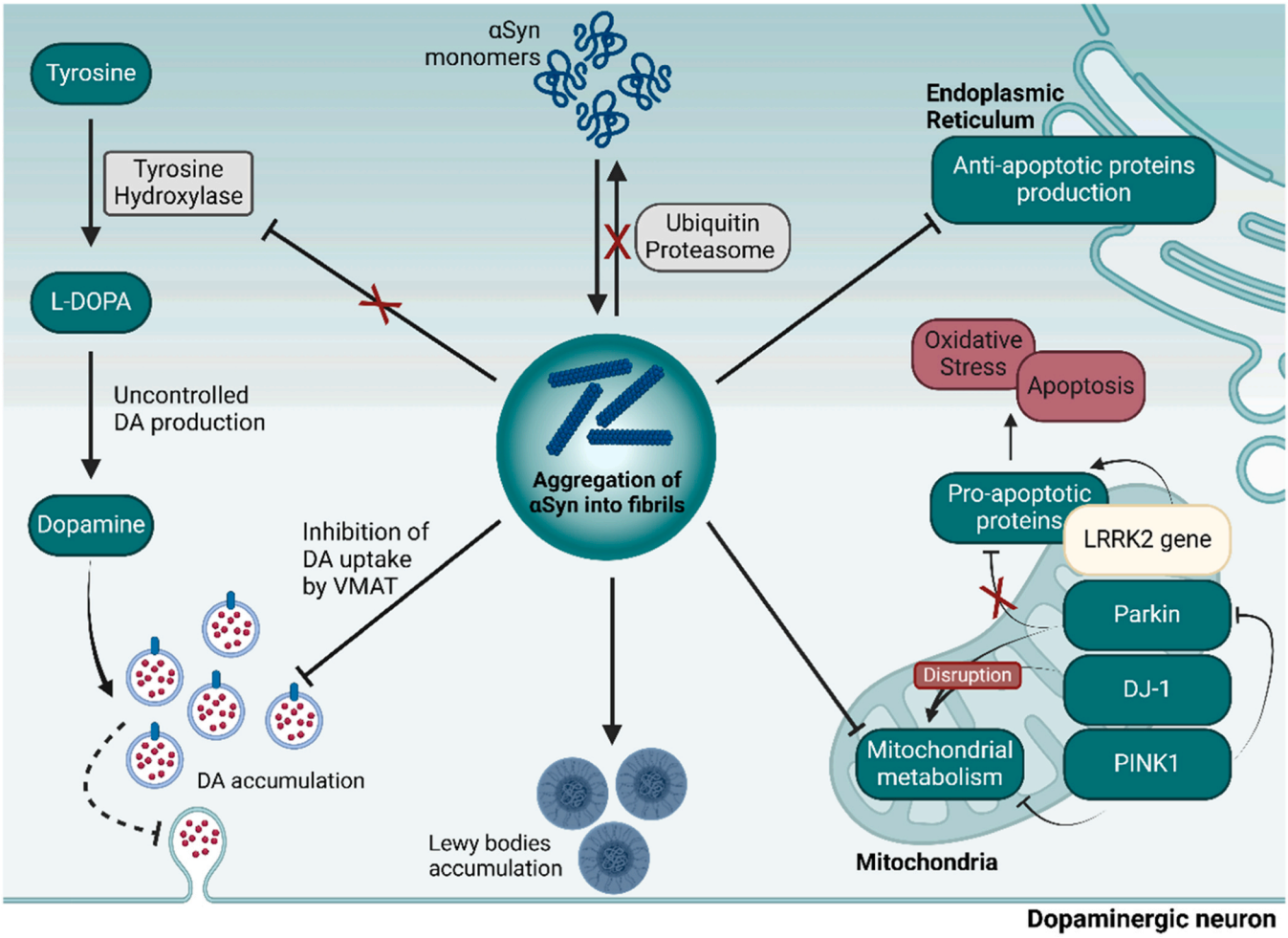


**Fig. 1.** Genetic alterations influencing (dopaminergic) neuron death. In a normal situation, αSyn is degraded through the ubiquitin-proteasome system, becoming soluble and allowing neuronal physiological functioning. αSyn binds to tyrosine hydroxylase (TH), inhibiting its activity and regulating DA synthesis. In PD, αSyn loses its function due to the aggregation into fibrils resulting in Lewy bodies accumulation and uncontrolled and toxic DA synthesis. Consequently, there is an inhibition of DA uptake by the vesicular monoamine transporter (VMAT) and a consequent DA accumulation in the neuron. Additionally, the αSyn fibrils accumulation will inhibit the activity of anti-apoptotic protein processing in the endoplasmic reticulum (ER). In the mitochondrial pathway, mutations in several genes lead to the deregulation of proteins involved in mitochondrial metabolism, mitophagy, and apoptosis, for example, the inhibition of the mitochondrial complex I and apoptotic proteins by PINK1, and Parkin and DJ-1, respectively. Moreover, a mutation in LRRK2 results in the overactivation of BAX (pro-apoptotic protein), which consequently, releases cytochrome c, which causes an increase in oxidative stress and apoptosis.

**Table 1**
Risk factors increasing the disease's incidence and prevalence.

| | Highest risk groups per condition | | | References |
|---|---|---|---|---|
| | **Parkinson's Disease** | **Chronic Kidney Disease** | **Cardiovascular Diseases** | |
| **Gender** | 3:2 male to female ratio of prevalence risk | More prevalent among women than men | More prevalent in men, but increased rate of mortality in women | (Kalia and Lang, 2015; Lewandowski et al., 2023; Suman et al., 2023) |
| **Age** | Older people and peak after 80 years of age. | High prevalence in the elderly, such that after 40 of age, GFR decreases by approximately 10 mL/min every decade. | High incidence and prevalence in older adults, with an incidence of about 86% in people above 80 years old. | (Kalia and Lang, 2015; Mallappallil et al., 2014; Rodgers et al., 2019) |
| **Environmental factor** | Individuals exposed to pesticide's use and environmental pollution | Individuals exposed to nephrotoxicants as metals, air pollution, and other chemicals as phthalates | Ischemic heart disease and stroke are responsible for 80% of the deaths related to the environmental pollution | (Kalia and Lang, 2015; Bloem et al., 2021; Tsai et al., 2021; Cosselman et al., 2015) |
| **Genetics** | 3–5% attributable to monogenic and 16–36% to non-monogenic genetic alteration | 25–44% of CKD cases are due to heritability | Familial hypercholesterolemia is the most common monogenic cause of CVD, with a frequency of 1:200 | (Bloem et al., 2021; Köttgen et al., 2022; Vrablik et al., 2021) |

loss of DAn.

Diagnosing PD is subjective and depends on the clinician's evaluation of the patient's phenotype. Currently, the most reliable method for an accurate diagnosis is the identification of LB deposits in the brainstem, limbic, and neocortical cerebral regions, along with observing the loss of DAn in SNpc through *post-mortem* histological examinations (Braak et al., 2003b; Wakabayashi, 2020; Kalia and Lang, 2015; Bloem et al., 2021; Reich and Savitt, 2019). Nevertheless, the

heterogeneity among patients poses a significant challenge for clinicians. According to the Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, many patients may exhibit similar symptoms, representing different forms of the disease and responding variably to treatments (Greenland et al., 2019; Berg et al., 2021). Consequently, searching for new and precise biomarkers is essential for achieving an earlier and more reliable diagnosis. The current treatment options for PD are limited, as available therapies only temporarily tackle and attenuate the symptoms without halting the progression of the disease. Such limitation may stem from the focus of PD research on replacing DA and stimulating its receptors, which may have overlooked critical pathophysiological concerns regarding the disease's progression and its adverse effects (Kalia and Lang, 2015; Bloem et al., 2021; Reich and Savitt, 2019). In addition to improving the treatment pipeline for PD, it is crucial to focus on two key areas: 1) developing new treatments or repurposing available ones to prevent disease progression, and 2) deepening our understanding of the pathophysiology of PD, particularly regarding its prodromic phase and peripheral connections. It is now widely accepted that PD is a complex and multifactorial condition, with other illnesses potentially influencing its onset and progression.

## 3. Cardiac dysfunction: a cause or a consequence of PD onset and progression?

Central anatomic network (CAN) areas are responsible for autonomic

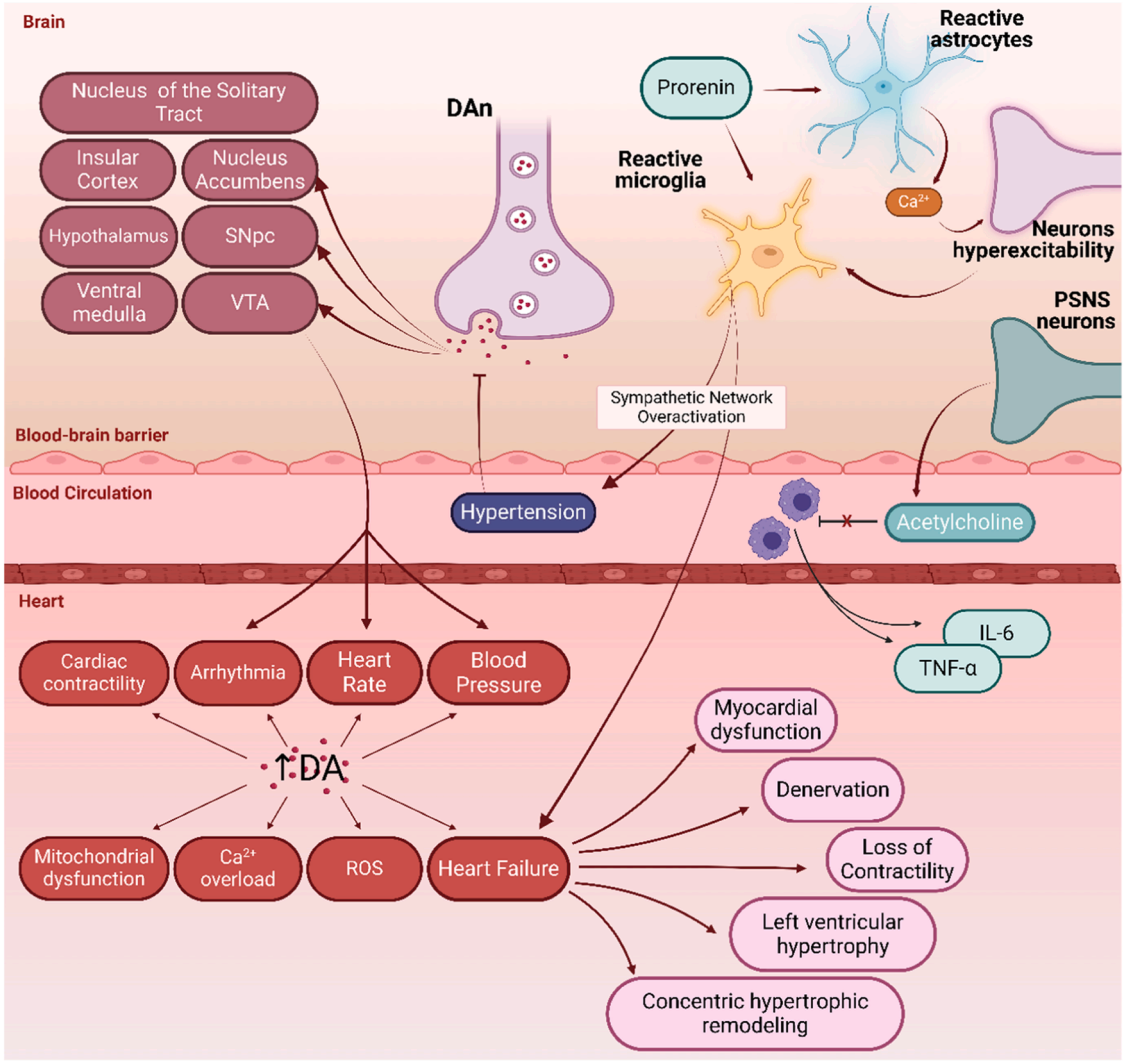


**Fig. 2.** Interactions between the brain and the heart in healthy and disease conditions. Key regions of the brain including the insular cortex, the hypothalamus, the nucleus of the solitary tract, and the ventral medulla are involved in the control of processes like heart rate and blood pressure as well as associated with cardiac complications such as arrhythmias in neurological disorders. The stimulation of the mesostriatal DAn modulates the information that reaches the nucleus accumbens, SNpc, and VTA regions, also leading to alterations in heart rate and BP. DA per se can enhance cardiac contractility and heart rate, and studies demonstrated that DA is capable of increasing cardiomyocyte activation, which can trigger HF-associated ventricular arrhythmia as well as promote $Ca^{2+}$ overload, mitochondrial dysfunction, ROS, and left ventricular impairments. Additionally, PD is often associated with HF, probably due to related issues such as myocardial dysfunction, denervation and loss of contractility, left ventricular hypertrophy, and hypertrophic remodeling derived from impaired ventricular relaxation. Chronic inflammation is a significant hallmark associated with both PD and CVD. In normal conditions, the release of acetylcholine by the PSNS suppresses the secretion of pro-inflammatory cytokines such as TNF-α or IL-6 by macrophages. This process plays a role in the inflammatory responses seen in both conditions. Furthermore, prorenin, a component of the RAS, has been shown to trigger a reactive response in microglia, subsequently prompting astrocytes to increase the release of gliotransmitters. In chronic astrocytic reactivity, high levels of $Ca^{2+}$ excitatory can occur, ending in the hyper-excitability of local neurons, which may contribute to sympathetic network dysfunction (overactivation), which could underlie the HF and hypertension triggering. DAn | Dopaminergic neurons; SNpc | Substantia Nigra pars compacta; VTA | Ventral Tegmental Area; BP | Blood pressure; DA | Dopamine; HF | Heart failure; ROS | Reactive Oxygen Species; PD | Parkinson's Disease; CVD | Cardiovascular Diseases; PSNS | Parasympathetic Nervous System; TNF-α | Tumor necrosis factor-α; IL-6 | Interleukin 6; RAS | Renin-Angiotensin system;.

and cardiovascular functions, including BP, the baroreflex mechanism, and heart rate (Benarroch, 1993). Key brain regions involved in these processes include the insular cortex, the hypothalamus, the nucleus of the solitary tract, and the ventral medulla (Fig. 2) (Cersosimo and Benarroch, 2013). These areas are particularly significant due to their involvement in the development of cardiac complications, such as arrhythmias and sudden death, in neurological diseases (Benarroch, 1993; Cersosimo and Benarroch, 2013; Iniguez et al., 2022). Research into the relationship between CVD and neurodegenerative disorders has been expanding (Song et al., 2021; Leszek et al., 2020), revealing shared characteristics. For instance, PD and CVD have common risk factors such as obesity, diabetes, oxidative stress, chronic inflammation, and hypertension (Cuenca-Bermejo et al., 2021; Acharya et al., 2020). As both PD and CVD have a rising incidence and prevalence, and knowing the high prevalence of CVD in PD patients, several studies have explored the potential association between these two conditions (Acharya et al., 2020). Zhongzheng Zhou and colleagues recently examined the genetic basis of this relationship, demonstrating that PD may be a possible pathogenetic factor for coronary artery disease and stroke (Zhou et al., 2023). In another large clinical study, a cohort study involving patients aged 40 and older, it was found that individuals with PD have a higher risk of CVD mortality compared to those without PD, and this association becomes even stronger with increasing age (Ke et al., 2024). From another point of view, studies conducted in spontaneous hypertensive rats (SHR), an animal model for hypertension, have shown impairments in the dopaminergic system, more specifically, a decrease in DA release and upregulation of D2 receptors in the striatum (Yeh et al., 2006; Van Den Buuse, 1997). Furthermore, Tzung-Lieh Yeh and colleagues found that the mesostriatal dopaminergic system plays a role in cardiovascular maintenance in healthy individuals (Yeh et al., 2006). For instance, it was suggested that the activation of the mesostriatal DAn modulates the information that reaches the nucleus accumbens, which is involved in regulating behavior, emotions, motivation, and ANS responses which are crucial for cardiovascular regulation (Fig. 2) (Yeh et al., 2006). Additionally, stimulating the mesotelencephalic dopaminergic pathway, particularly in the SNpc and ventral tegmental area regions, can lead to alterations in heart rate and BP (Fig. 2) (Yeh et al., 2006). Nevertheless, some authors argue that DA does not directly affect BP but modulates cardiovascular reflexes' sensitivity (such as the heart rate reflex) (Yeh et al., 2006). While the PSNS may play a role in the relationship between the striatal DAn, concerning cardiovascular function and the BP, the precise mechanism behind this interaction is still unclear and requires further investigation. In the context of heart failure (HF), DA can be used to manage the condition by altering the force of myocardial contractions, heart rate (HR), and constriction of the coronary arteries (Neumann et al., 2023). However, the effects of DA vary depending on the cardiac pathology involved. Of note, in moderate doses (4-10 $\mu g \cdot kg^{-1} \cdot min^{-1}$), DA *per se* can enhance cardiac contractility and heart rate due to its positive inotropic and chronotropic actions (Hiemstra et al., 2019; Doggrell, 2002). Notwithstanding, Yamaguchi and coworkers demonstrated in their recent preclinical study that administering higher doses of DA (20 mg/kg) to induce arrhythmia leads to D1 receptor overexpression and increased cardiomyocyte activation, which can trigger HF-associated ventricular arrhythmia (Yamaguchi et al., 2020). Additionally, elevated plasma levels of DA in cases of Takotsubo cardiomyopathy can result in calcium ($Ca^{2+}$) overload, mitochondrial dysfunction, reactive oxygen species (ROS), left ventricular impairments, and high mortality rates (Fig. 2) (Nakagawa et al., 2016; Pelliccia et al., 2017; Bucolo et al., 2019; van Weperen et al., 2023). These outcomes are likely due to excessive activation of dopaminergic receptors (DR) activation affecting both myocardial and microcirculatory functions (Nakagawa et al., 2016; Pelliccia et al., 2017; Bucolo et al., 2019; van Weperen et al., 2023). Being so this relationship may be linked to DA's ability to increase L-type $Ca^{2+}$ currents (Bucolo et al., 2019). One potential molecular explanation for this effect involves the phosphorylation of L-type $Ca^{2+}$ channels through the cyclic adenosine monophosphate (cAMP) – protein kinase A (PKA) signaling pathway (Bucolo et al., 2019). This process is primarily mediated by the Gs subunit of G protein, which couples with to adenylyl cyclase following D1R stimulation by DA or other agonists (Bucolo et al., 2019). Given the dual role of DA in HF, there is ongoing debate regarding whether this drug produces beneficial or harmful effects (Hiemstra et al., 2019; Yamaguchi et al., 2020; Hampton et al., 1997; Massel et al., 1997). From a different perspective, levodopa is considered the gold standard for symptomatic treatment of PD, as it aims to restore the levels of DA. Some preclinical and clinical studies have examined the effects of this therapy in the cardiovascular context (Silva et al., 2015; Günaydın et al., 2016; Noack et al., 2014). Nevertheless, no significant cardiac alterations were observed when comparing the PD groups with and without this therapy.

Independently of the CVD risk factors, PD patients have twice the prevalence of HF compared to the general population, with retrospective cohort studies revealing that HF is associated with an increased risk of idiopathic PD (Brokowski, 2019). Additionally, HF is one of the leading causes of mortality among PD patients (Piqueras-Flores et al., 2018; Mukherjee et al., 2015). This increased prevalence may be linked to several complications associated with PD, including myocardial dysfunction, denervation and loss of contractility, left ventricular hypertrophy, and consequent concentric hypertrophic remodeling (Cuenca-Bermejo et al., 2021; Piqueras-Flores et al., 2018; Byku and Mann, 2016). This remodeling is characterized by increased left ventricular relative wall thickness while maintaining normal ventricular dimensions, accompanied by diastolic dysfunction due to impaired ventricular relaxation (Fig. 2). Most PD patients also experience cardiac autonomic dysfunction (CAD) and cardiac denervation (CD), caused by the loss of sympathetic (noradrenergic nerves) and parasympathetic supply, as well as extra-cardiac noradrenergic denervation and arterial baroreflex failure (Fig. 2) (Scorza et al., 2018; Jain and Goldstein, 2012; Cuenca-Bermejo et al., 2021; Hong et al., 2019). CAD and CD are typically accessed by heart-rate variability (HRV), which measures the fluctuation in the time intervals between successive heartbeats. The loss of sympathetic and parasympathetic innervation leads to postprandial hypotension, decreased HRV, and orthostatic hypotension, facts currently known to contribute to CAN dysfunctions (Benarroch, 1993; Cersosimo and Benarroch, 2013; Iniguez et al., 2022; Piqueras-Flores et al., 2018; Ding et al., 2020). Interestingly, a recent study by Iniguez and colleagues revealed that idiopathic PD patients exhibit a functional disconnection between heart function and CAN activity (Iniguez et al., 2022). This disconnection occurs even after excluding confounding factors such as diabetes mellitus, hemodynamic alterations, or other neurologic complications. The study suggests a desynchronization between HRV and blood oxygenation levels in several brain areas belonging to the CAN, including the cerebellum, brainstem, lateral parietal-temporal cortex, medial prefrontal cortex, insula, hypothalamus, and anterior cingulate cortex.

Chronic inflammation is a main hallmark associated not only with CVD but also with PD. Clinical studies have shown that by modulating the inflammatory response, the occurrence of stroke and CAD can be reduced (Henein et al., 2022; Kelly et al., 2021). The release of acetylcholine by the PSNS, which usually suppresses the secretion of pro-inflammatory cytokines such as Tumor necrosis factor - α (TNF-α) or Interleukine-6 (IL-6) by macrophages, has been enrolled in this process (Fig. 2) (Henein et al., 2022; Andersson, 2005). Interestingly, prorenin, a renin-angiotensin system (RAS) component, has been found to trigger a reactive response in microglia, which are the primary immune cells in the CNS (Fig. 2). This will prompt astrocytes to increase the release of gliotransmitters – compounds released by glial cells in response to stimuli -, such as ATP, glutamate, and gamma-aminobutyric acid (GABA), among others (Fig. 2). In chronic astrocytic reactivity, elevated levels of $Ca^{2+}$ excitation waves are released, resulting in the hyper-excitability of local neurons (Fig. 2) (Marina et al., 2016). Through these mechanisms, glial cells can contribute to sympathetic

network overactivation, which is on the basis of HF and hypertension (Fig. 2). In fact, the term "Parkinsonian heart" arose as a consequence of the prevalence of features such as HF, CAD, CD, and chronic inflammation among PD patients. In the last few years, this term has gained significant attention, with additional hemodynamic and cardiovascular changes supporting the potential existence of a brain-heart axis in PD. One of the most frequent cardiac-related alterations in PD patients is orthostatic hypotension, characterized by a decrease in blood pressure after rising from a supine position to a head-up position, which is strongly associated with cardiac denervation (Piqueras-Flores et al., 2018). Research indicates that orthostatic hypotension is associated with dysfunction in both sympathetic and parasympathetic systems, likely resulting from insufficient levels of noradrenaline (NA) (Fig. 2). This catecholamine neurotransmitter is critical in the sympathetic nervous system (SNS) (Jain and Goldstein, 2012; Titova et al., 2017; Kalia and Lang, 2015). NA also innervates the vascular system and the heart, and stimulates adrenergic receptors (Jain and Goldstein, 2012; Titova et al., 2017; Kalia and Lang, 2015). Along with DA, a loss of NA has been associated with the early stages and progression of PD (Cuenca-Bermejo et al., 2021). The connection may stem from both neurotransmitters sharing the same biosynthetic pathway (Cuenca-Bermejo et al., 2021). Nevertheless, the exact mechanism through which SNS deteriorates remains unclear. It is still uncertain whether this deterioration is due to the degeneration of CNS neurons or the loss of peripheral sympathetic fibers (Cuenca-Bermejo et al., 2021; Titova et al., 2017; Fornai et al., 2007).

Recent research from Acharya and colleagues, using body fluid samples such as cerebrospinal fluid, serum, and plasma of PD patients, has shown that specific non-coding RNAs are altered in PD and CVD (Acharya et al., 2020). Specifically, miR-133b regulates the development of midbrain DAn and reduces the production of ROS after myocardial infarction. Furthermore, several other microRNAs are noteworthy: miR-124, downregulated in PD; miR-124–5p, unstable; and miR-124–3p upregulated in PD. These microRNAs protect against cardiac injury and neuroinflammation, exhibiting antioxidant properties (Acharya et al., 2020). Specifically, miR-124 can inhibit neuroinflammation through the MEKK3/NF-κB signaling pathway or enhance superoxide dismutase activity, thereby providing protective effects against neuroinflammation and oxidative stress (Yao et al., 2018). MALAT1 (Metastasis Associated Lung Adenocarcinoma Transcript 1) is found to be upregulated in PD and also acts as a critical promotor of cardiomyocyte and DAn apoptosis, as well as contributing to cardiac fibrosis and αSyn expression (Acharya et al., 2020). This makes MALAT1 a potential target for modulating apoptosis. Overall, understanding the pathophysiological roles of non-coding RNAs is essential, as this knowledge could lead to their use as potential biomarkers and therapeutic targets in the context of illness onset and progression.

While considerable evidence suggests a potential cause-effect relationship between the brain and the heart, as well as associated diseases, the underlying mechanisms facilitating communication between these two organs are still largely unknown. Critical questions regarding the prognosis and molecular characteristics such as DAn degeneration and neuroinflammation - of CVD patients with PD remain unsolved. Therefore, gaining a better understanding of this interaction and how we can influence it may ultimately lead to the discovery of new (bio)markers or targets for synergistic treatment of various disease conditions.

## 4. What about renal dysfunction and Parkinson's disease?

Chronic kidney disease (CKD) is expected to become the 5th leading cause of death by 2040 and the most frequent chronic condition among older patients. CKD is frequently linked with several co-occurring health conditions. Diagnosis typically relies on assessing the reduced estimated glomerular filtration rate (eGFR) and albuminuria (i-e., the presence of albumin in the urine) (Meléndez-Flores and Estrada-Bellmann, 2021; Safarpour et al., 2021; Baba et al., 2011). In patients with CKD, specifically those with end-stage renal disease (ESRD), there are usually dysfunctions affecting the CNS, PSNS, and ANS (Hamed, 2019). These complications include cognitive impairment, encephalopathy, cerebrovascular stroke, restless leg syndrome, and parkinsonism. Many studies suggest that chronic renal dysfunction is directly associated with PD, constituting an independent risk factor for this disease (Nam et al., 2019; Hamed, 2019). Notably, a recent clinical study involving a cohort of patients diagnosed with CKD found that CKD in middle-aged and older patients is associated with an increased risk of developing PD (Kim, 2024). Another prospective cohort study revealed that reduced eGFR is significantly associated with a heightened risk of PD, particularly with brain volume atrophy in areas linked to the disease (Peng et al., 2024). Therefore, monitoring key markers of renal function, such as proteinuria and eGFR, is recommended for the early detection of PD (Nam et al., 2019; Qu et al., 2023). In addition, it should be highlighted that DAn are not the only source of DA. Although DA does not cross the blood-brain barrier (BBB), the proximal tubule cells also synthesize it peripherally in the kidneys (Qaddumi and Jose, 2021). Additionally, the kidney expresses DR, including all the subtypes of DR expressed in the proximal tubule, distal convoluted tubule, and cortical collecting duct (Qaddumi and Jose, 2021). Specifically, D1R and D3R were found in macula densa and juxtaglomerular cells (Qaddumi and Jose, 2021). In the medullary thick ascending limb, D1R, D3R, D4R, and D5R are expressed, while D3R is found in the cortical thick ascending limb (Qaddumi and Jose, 2021). Functionally, studies have pointed out that the renal dopaminergic system plays a crucial role in regulating BP and its activity increases in response to salt overload from dietary intake (Doggrell, 2002; Qaddumi and Jose, 2021; Choi, 2015). Nevertheless, dopaminergic control has reduced activity in salt-sensitive hypertensive patients and rats, with evidence suggesting the involvement of D3R (Doggrell, 2002; Qaddumi and Jose, 2021). Dysfunction within the renal dopaminergic system has been associated with impaired kidney function. Specifically, a compromised renal dopaminergic system is associated with increased expression of tubular sodium transporters, oxidative stress, inflammation, elevated levels of renin, and an increase in Angiotensin II (Ang II) Type I Receptor (AT1R) expression (Qaddumi and Jose, 2021). The situation leads to renal injury and a reduction in Ang II Type II Receptor (AT2R) and Mas Receptor (MasR) expressions, ultimately influencing natriuresis (sodium excretion in the urine) and diuresis, which are suggested to be associated with hypertension pathology (Qaddumi and Jose, 2021). In CKD, RAS becomes overactivated due to SNS stimulation, causing an increase in Ang II and its binding to AT1R (Meléndez-Flores and Estrada-Bellmann, 2021). Additionally, the kidneys are supplied with an extensive network of sympathetic (efferent) neurons that relay signals from the sympathetic ganglia to the kidneys (Osborn and Foss, 2017). Remarkably, Osborn and colleagues have explained that heightened efferent renal nerve activity stimulates inflammatory cascades, which can lead to renal impairment and hypertension (Osborn and Foss, 2017). This highlights a close and intriguing relationship between the nervous and immune systems and the development of hypertension (Osborn and Foss, 2017).

Finally, oxidative stress and mitochondrial impairment are significant players in the pathophysiology of both CKD and PD. These conditions cause lipid peroxidation-associated membrane damage, protein oxidation, structure, function alterations, and structural DNA damage, hallmarks commonly seen in neurodegenerative diseases and renal damage (Adesso et al., 2017). Research shows that increased expression and activation of AT1R in the striatum and substantia nigra, along with increased ROS and oxidative stress, contribute to (DAn) neuronal damage (Meléndez-Flores and Estrada-Bellmann, 2021). In fact, it has been described that ROS interacts with nitric oxide, leading to the production of toxic substances such as uremic toxins (UTs), which significantly affect kidney function (Meléndez-Flores and Estrada-Bellmann, 2021; Safarpour et al., 2021; Hamed, 2019; Liabeuf et al., 2021). Indeed, it is hypothesized that during renal impairment, the receptors for UT in the BBB and blood-cerebrospinal fluid barrier increase, resulting in the accumulation of UT in the brain (Assem et al.,

2018). This accumulation is thought to be a leading cause of cognitive impairment associated with CKD (Adesso et al., 2017), with symptoms ranging from mild issues, such as poor concentration, short attention span, recent memory dysfunction, apathy, and depression, to more severe conditions, including significant memory loss, executive function deficits, and dementia (Hamed, 2019; Bossola and Picconi, 2024).

Additionally, UT in the brain is associated with DNA and protein damage (Fornai et al., 2007), and with activation of neuroinflammatory and oxidative pathways (Safarpour et al., 2021), which are common mechanisms in PD. These conditions also inhibit the antioxidant and cytoprotective systems, cause apoptosis, and disrupt the BBB (Safarpour et al., 2021; Hamed, 2019; Adesso et al., 2017).

## 5. The brain-heart-kidney axis: is there a link between CVD, CKD, and PD?

As previously discussed, BP and water balance are controlled by the kidneys, the heart, and the brain which work in tight coordination attained to ANS-regulated hormonal and neuronal mechanisms. Hypertension is a common risk factor linked to the development of PD, CVD, and CKD (Meléndez-Flores and Estrada-Bellmann, 2021; Rangaswami et al., 2019). However, the mechanisms engaged in these relationships still need to be explored. Some authors argue that high BP decreases resting cerebral blood flow, which in turn reduces the delivery of oxygen (Hou et al., 2018). This is particularly important in regions that are sensitive to ischemia, such as the substantia nigra, resulting in DAn loss (Hou et al., 2018).

The RAS is critical in regulating BP, water, electrolyte balance, and overall cardiovascular homeostasis (Cosardereliogl u et al., 2020; Abiodun and Ola, 2020; Jackson et al., 2018). Under physiological conditions, the kidneys produce renin, which cleaves the angiotensinogen to release angiotensin I (Ames et al., 2019). The angiotensin-converting enzyme (ACE) converts this angiotensin I into Ang II (Ames et al., 2019). Ang II can bind to two receptors: the AT1R or AT2R (Ames et al., 2019). For instance, when Ang II binds to AT1R, it triggers various pathophysiological processes, including pro-oxidative, pro-inflammatory, and pro-fibrotic responses. In contrast, binding to AT2R, which has a higher expression in the brain - particularly in areas controlling BP – may trigger opposite effects (Cosardereliogl u et al., 2020; Abiodun and Ola, 2020; Jackson et al., 2018). Subsequently, the angiotensin-converting enzyme 2 (ACE 2) converts Ang II into angiotensin (1−7), which finally interacts with MasR, resulting in vasodilatation and prompting anti-inflammatory and anti-oxidative effects. Interestingly, in addition to the peripheral RAS, a local brain RAS has also been identified (Meléndez-Flores and Estrada-Bellmann, 2021; Cosardereliogl u et al., 2020; Abiodun and Ola, 2020; Jackson et al., 2018; Loera-Valencia et al., 2021). This local RAS is involved in oxidative stress, polarization of microglia cells, neuroinflammation, and brain homeostasis (Meléndez-Flores and Estrada-Bellmann, 2021; Cosardereliogl u et al., 2020; Abiodun and Ola, 2020; Jackson et al., 2018; Loera-Valencia et al., 2021). Due to the BBB, the brain possesses active RAS genes and the capability for *de novo* proteins production to support its RAS needs (Cosardereliogl u et al., 2020; Abiodun and Ola, 2020; Jackson et al., 2018). Additionally, increased RAS activity has been linked to DAn degeneration in PD conditions involving oxidative stress and neuroinflammation. However, the precise mechanisms underlying this specific relationship need to be elucidated (Song and Kim, 2016).

Likewise, autophagy is a crucial mechanism for the degradation and recycling of misfolding proteins, dysfunctional organelles, and cytosolic components (Nechushtai et al., 2023). This process can occur through macroautophagy, microautophagy, or chaperon-mediated autophagy (Nechushtai et al., 2023), playing a significant role in maintaining renal, cardiac, and cerebral function and homeostasis; nonetheless, it is also involved in various pathological conditions (Nechushtai et al., 2023; Bhatia and Choi, 2020; Lavandero et al., 2015). Meanwhile, defective autophagy has been associated with neurodegenerative disorders, including PD, where it leads to neurotoxic accumulation and aggregation of proteins, such as αSyn (Fig. 3) (Nechushtai et al., 2023; Zhu et al., 2022). Besides being involved in neuroinflammation, microglia play a crucial role in the autophagic process, carrying αSyn aggregates into lysosomes and forming autophagosomes as part of phagocytosis (Fig. 3) (Zhu et al., 2022). Furthermore, autophagy has also been associated with CKD, particularly renal fibrosis, playing a double-edged sword role by exerting profibrotic and anti-fibrotic functions (Bhatia and Choi, 2020). Increased expression of autophagic markers in well-established models of renal fibrosis has shown protective features (Bhatia and Choi, 2020). However, persistent activation of autophagy can also result in the accumulation of extracellular matrix components (Fig. 3). Transforming growth factor β1 (TGF-β1), known to trigger inflammatory, fibrotic, and cell cycle regulatory pathways, was described to play an ambiguous role, acting either as an inducer or an autophagy inhibitor (Bhatia and Choi, 2020; Ruby et al., 2023). For instance, TGF- β1 activates autophagy-related genes (such as Atg5, Atg7, LC3, and Beclin 1) while also acting through the PI3K/AKT pathway, negatively regulating autophagy. Therefore, the factors determining whether it promotes or inhibits autophagy require further elucidation (Bhatia and Choi, 2020; Ruby et al., 2023). This intricate relationship between autophagy, renal fibrosis, and the role of TGF-β1 indicates potential therapeutic targets worth exploring. Similarly, Lavandero and colleagues explained how autophagy can be protective or detrimental in CVD (Lavandero et al., 2015). While autophagy regulates the structure and function of cardiomyocytes under normal conditions, excessive activation can lead to HF in pathological scenarios (Fig. 3) (Lavandero et al., 2015). Autophagy helps to clear damaged mitochondria, which are abundant in cardiomyocytes, thereby preventing the activation of apoptosis (Nishida et al., 2009). However, in severe circumstances, such as cardiac ischemia/reperfusion, excessive autophagy activationcan cause organelles' degradation and release pro-apoptotic factors, ultimately leading to cell death (Fig. 3) (Nishida et al., 2009). As such, given the significance of autophagy in these three organs, whether in healthy or diseased states, it may play a role in overall axis function. Nevertheless, this possibly requires further investigation.

Finally, $Ca^{2+}$ plays a crucial role in regulating various cellular and molecular biological processes, connecting renal, cardiac, and (PD) brain functions, including cell proliferation, motility and signaling, neuronal regulation, and mechanisms related to autophagy and apoptosis. This regulation is attained because $Ca^{2+}$ regulates action potentials, enzymatic activity, signal transduction, and gene transcription (Zhou and Greka, 2016; Clapham, 2007). In the brain, astrocytes release gliotransmitters, such as ATP, glutamate, or GABA, in response to G-protein-coupled receptors. When these proteins are activated, they trigger intracellular $Ca^{2+}$ responses (Araque et al., 2014). As an astrocytic gliotransmitter, ATP, enhances $Ca^{2+}$ excitation waves propagating through adjacent astrocytes (Araque et al., 2014). The modulation of $Ca^{2+}$ signals affects the excitability of local neuronal circuits, synaptic transmission and plasticity (Marina et al., 2016; Tedoldi et al., 2021; Chandran et al., 2019). In addition to neurons and astrocytes, ATP interacts with purinergic receptors on endothelial and blood cells (Tedoldi et al., 2021). This interaction alters the intracellular $Ca^{2+}$ concentration and can lead to vasodilation or vasoconstriction of blood vessels (Tedoldi et al., 2021). In fact, in the heart, an action potential allows the opening of the L-type channels leading to the entrance of $Ca^{2+}$ in the cells. This influx leads to the release of additional $Ca^{2+}$ from the sarcoplasmic reticulum (SR) through a process known as "calcium-induced calcium release", which is essential for heart contraction (Eisner et al., 2020; Eisner, 2014; Endo, 1977). Conversely, the concentration of $Ca^{2+}$ decreases due to the action of SR $Ca^{2+}$-ATPase, which transports $Ca^{2+}$ back into the SR (Eisner et al., 2020; Eisner, 2014). Additionally, a cooperative mechanism involving $Na^{+}$-$Ca^{2+}$ exchanger and plasma membrane $Ca^{2+}$-ATPase also helps remove $Ca^{2+}$ from the cell (Eisner et al., 2020; Eisner, 2014). This process utilizes the energy generated

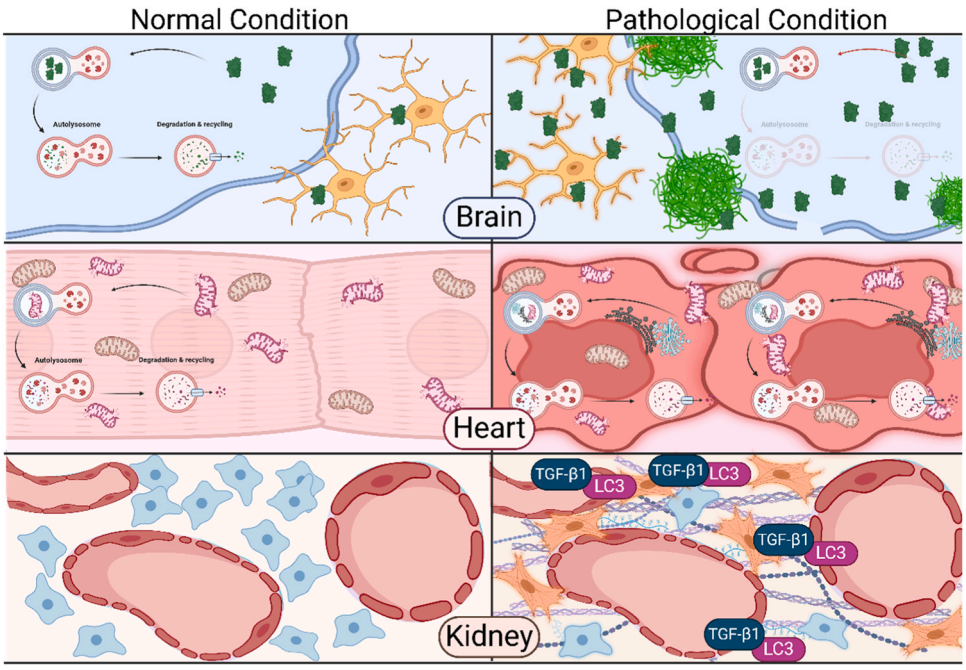


**Fig. 3.** The role of autophagy in the brain-heart-kidney axis. Autophagy is an essential mechanism for removing misfolding proteins, dysfunctional organelles, and cytosolic components, thereby maintaining proper function and homeostasis in the kidneys, heart, and brain. Nonetheless, this process can also be associated with pathological features in these systems. Defective autophagy has been associated with PD, leading to neurotoxic accumulation and aggregation of proteins, such as αSyn. Microglia plays a significant role in both neuroinflammatory and the autophagic process, where αSyn aggregates into lysosomes and forms autophagosomes as part of phagocytosis. Regarding CVD, precisely regulating the extent of autophagy is crucial for the homeostasis and proper function of cardiomyocytes. Under normal conditions, the autophagic process serves a protective role by clearing damaged mitochondria, which helps prevent apoptosis. However, in severe conditions like cardiac ischemia/reperfusion, excessive activation of the autophagy demand results in significant degradation of organelles and the release of pro-apoptotic factors, ultimately resulting in cell death. Autophagy is also implicated in CKD, particularly in renal fibrosis, where its role is more complex. It plays a double-edged sword role by exerting profibrotic and anti-fibrotic functions. Persistent activation of autophagy, characterized by increased expression of LC3 protein (a component of the autophagosome's membranes), can lead to the accumulation of extracellular matrix. In this context, TGF-β1 has been observed to have an ambiguous role, acting either as an inducer or as an autophagy inhibitor. TGF-β1 | transforming growth factor β1; LC3 | Microtubule-associated protein 1 A/1B-light chain 3; PD | Parkinson's Disease; αSyn | alpha-synuclein; CVD | Cardiovascular Disease; CKD | Chronic kidney disease.

from entering of three $Na^+$ ions into the cell, simultaneously pumping out the $Ca^{2+}$ through an electric impulse (Eisner et al., 2020; Eisner, 2014). This balance is critical for the heart to relax properly. Nevertheless, it is essential to highlight that the amount of $Ca^{2+}$ entering the cells must equal the amount leaving in order to maintain homeostasis. The increase in intracellular $Ca^{2+}$ concentration arises from both the heightened current through L-type channels and the amount of $Ca^{2+}$ stored in SR (Eisner et al., 2020; Eisner, 2014). Therefore, $Ca^{2+}$ signaling and homeostasis are critical for the heart's and the entire organism's structural and physiological function as they are crucial for effective blood pumping.

Concomitantly, $Ca^{2+}$ in the blood and extracellular fluids are filtered and reabsorbed in the kidneys, the gut, and the bones, where $Ca^{2+}$ can also be deposited) (Zhou and Greka, 2016). In the kidneys, $Ca^{2+}$ filtration is achieved through two tightly regulated pathways, namely: paracellular and the transcellular. When the filtrate enters the nephron and moves through the tight junctions of epithelial cells (the paracellular route), $Ca^{2+}$ is reabsorbed, decreasing its concentration in the fluid until it reaches the proximal tubule. Once in the loop of Henle, both descending and ascending limbs are impermeable to $Ca^{2+}$, which activates the transcellular route in the distal convoluted tubule (Zhou and Greka, 2016; Hanna et al., 2022). Here, $Ca^{2+}$ enters the apical membrane through ion channels, diffuses to the basolateral membrane by binding to proteins and buffers, and then exits through the basolateral membrane's pumps or exchangers (Zhou and Greka, 2016; Hanna et al., 2022). The paracellular route is more efficient, allowing for a greater quantity of filtrate, while the transcellular pathway offers precise regulation of $Ca^{2+}$ concentration (Zhou and Greka, 2016). In the end, any excess of $Ca^{2+}$ that exceeds the body's homeostatic needs is excreted through urine.

$Ca^{2+}$ specific channels, transporters and pumps attain intracellular concentration. Different types of $Ca^{2+}$ channels differ in their voltage dependence, location, and kinetics. For instance, L-type channels are found in cardiac myocytes and are characterized by slower voltage-dependent inactivation. These channels are associated with the $Ca_v1$ calcium channel subtype and can be blocked by dihydropyridine drugs. In contrast, T-type channels are transient and are present in both the sinoatrial node's cardiac myocytes and thalamic neurons. These channels are associated with the $Ca_v3$ calcium channel subtype. Additionally, various types of calcium channels related to the $Ca_v2$ calcium channel subtype have been identified in neurons (Matsubara et al., 2010; Huang et al., 2022; Marras et al., 2012)–159].

Remarkably, the dysregulation of $Ca^{2+}$ is a well-recognized hallmark of PD. In a healthy condition, DAn enhances the activation of L-type calcium channels through DA-associated stimulation. In contrast, these channels activate spontaneously under PD, significantly increasing intracellular $Ca^{2+}$ (Ludtmann and Abramov, 2018; Augustine et al., 2003; Vaarmann et al., 2010; Surmeier and Schumacker, 2013). The DAn in substantia nigra pars compacta (SNpc) exhibits physiological and spontaneous pacemaking activity, which is involved in $Ca^{2+}$ influx through L-type channels. Slight increases in this $Ca^{2+}$ influx have been shown to promote mitochondrial oxidative stress, making DAn more vulnerable to degeneration (Pchitskaya et al., 2018; Guzman et al., 2009; Puopolo et al., 2007; Chan et al., 2007; James Surmeier et al., 2012; Surmeier et al., 2017). Additionally, αSyn, whether in a monomeric or oligomeric form, promotes the formation of pores in the plasma membrane by binding to vesicle membranes and forming porous structures. This contributes to the transport of $Ca^{2+}$ from extracellular space

into the cell (Ludtmann and Abramov, 2018; Angelova et al., 2016; Kayed et al., 2004; Zakharov et al., 2007). Conversely, the role of $Ca^{2+}$ in the development and progression of CKD and CVD is not fully understood, and the available studies often present contradictory findings. Some authors argue that $Ca^{2+}$ levels and disease progression or stage are independent variables in CKD and ESRD patients. On the other hand, some studies have shown that lower calcium levels are associated with poorer kidney function and higher mortality rates (Block and Port, 2003; Foley et al., 1996; Janmaat et al., 2018; Schwarz et al., 2006; Lim et al., 2014). Despite these inconsistencies, certain features regarding $Ca^{2+}$-associated kidney impairments are generally accepted when describing CKD patients. These include: i) a prevalence of mineral metabolism disturbances characterized by decreased calcium serum, urinary, and absorption levels, which contributes to the deterioration of kidney function; and ii) vascular and soft tissue calcification, which can lead to cardiovascular events (Janmaat et al., 2018; Palmer et al., 2011; O'Neill, 2016; Moorthi and Moe, 2011; Hill Gallant and Spiegel, 2017; Shanahan et al., 2011).

Consequently, drugs targeting these channels, known as calcium channel blockers (CCB), have garnered significant attention in recent years for the treatment of hypertension and arrhythmias. CCBs prevent $Ca^{2+}$ influx through L-type channels, resulting in vasodilation and decreased BP (Shah et al., 2022; Frishman, 2007; Elliott and Ram, 2011; Ohno et al., 2022). There are two main types of CCB: i) dihydropyridine CCB, which acts predominantly in vasodilation, such as amlodipine, nifedipine, nicardipine, and felodipine, and ii) non-dihydropyridine, which act predominantly in heart functioning, including verapamil and diltiazem (Frishman, 2007; Elliott and Ram, 2011; Ohno et al., 2022). Recently, numerous studies have focused on the possible repurposing effects of these drugs, such as their potential to prevent inflammation, necrosis, fibrosis, and protein aggregation by enhancing autophagy (Matsubara et al., 2010; Huang et al., 2022; Siddiqi et al., 2019). The term "drug repurposing" has recently sparked interest in the scientific community, presumably due to the potential benefits of using existing pharmaceuticals for new therapeutic purposes, especially, mainly for diseases affecting a vast range of the worldwide aged population, such as PD, CVD, and CKD. Actually, basic and clinical research has indicated that some anti-hypertensive drugs, including CCBs, exhibit neuroprotective properties, making them beneficial for neurodegenerative disorders (Huang et al., 2022; Siddiqi et al., 2019; Marras et al., 2012). For instance, Siddiqi and colleagues demonstrated that Felodipine, an L-type CCB, at doses like those found in human plasma, significantly influences neuroinflammation and glial activity. Furthermore, it can effectively clear mutant αSyn in mouse brains through an autophagy-dependent mechanism, providing neuroprotection and emerging as a promising therapeutic option for PD (Siddiqi et al., 2019). Similarly, Amlodipine, another dihydropyridine, and L-type CCB has shown comparable benefits to Felodipine, including the upregulation of autophagy (Huang et al., 2022). However, despite its longer plasma half-life, amlodipine does not cross the BBB, creating the challenge of its local effects on the brain (Siddiqi et al., 2019). Therefore, understanding the role of autophagy in PD, CVD, and CKD is critical, particularly regarding the modulation of autophagy by CCBs and its potential impact on the overall function of these conditions. Given the involvement of $Ca^{2+}$ in PD, CKD, and CVD, along with the promising strategies involving CCBs, it is essential to deepen our understanding of the mechanisms of $Ca^{2+}$ dysregulation hypothetically linking these pathologies.

Altogether, considering the various physiological mechanisms shared by these three organs, either in healthy or pathological contexts, it is reasonable to assume that the deregulation of one mechanism could affect the proper functioning of more than one organ. Therefore, it becomes critical to determine whether alterations in just one mechanism in one organ are sufficient to cause dysfunction in another organ within this axis or whether several alterations are required for dysfunction to occur. By doing so, new avenues for early (disease) detection or treatment through new biomarkers or therapeutic targets could be established.

## 6. Conclusion and future perspectives

Several clinical and biochemical pieces of evidence support the existence of complex brain-heart-kidney interactions that are critical for maintaining overall homeostasis. Key factors such as the dopaminergic system, BP, RAS, chronic inflammation, autophagy, oxidative stress, and $Ca^{2+}$ signaling play significant roles in each organ's (patho)physiology. However, these factors may also be important game changers when considering the brain-heart-kidney axis as a whole. Dysfunction in any part of this axis could lead to a broad spectrum of significant health problems affecting the other two organs. In current clinical practice, the connections between peripheral illnesses and central nervous system problems are gaining notable consideration, and researchers are investigating these relationships across several conditions. With precision medicine technological advancement, the *one-disease-one-target* concept is no longer a reality, and nowadays, a multifactorial and multiorgan connection is a more probable possibility. Nevertheless, further studies are necessary to fully understand how diseases in one organ may influence the health of others, as well as to clarify the causal relationships between diseases in this axis. To the best of our knowledge, currently, there are no available models to study PD, CVD, and CKD simultaneously. However, there is an opportunity to leverage existing models to investigate how one disease may influence the others and trigger their onset. For example, there are numerous animal models of PD in which the kidney and heart functions could be effectively assessed. On the other hand, examining, for instance, brain dopaminergic innervation integrity in models of CRS could yield valuable insights. Moreover, creating a model that disrupts the function of all organs within this interconnected axis—by combining PD and CRS animal models—would significantly enhance our understanding of their interactions. Additionally, *in vitro* models, particularly those using microfluidics can uncover essential cellular and molecular mechanisms that underline these complex interconnections. Pursuing this can pave the way for groundbreaking discoveries about these diseases' relationships. Insights gained from this research could help identify novel biomarkers for detecting diseases at early stages, potentially delaying disease progression or clinical manifestation in high-risk patients. Additionally, repurposing existing medications, such as CCB for new therapeutic uses could offer new perspectives for modulating the intricate systems with the brain-hear-kidney axis.

## Author statement

All authors have reviewed and approved the final revised version for resubmission to the Brain Organoid Systems Neuroscience Journal.

## CRediT authorship contribution statement

**Cristiana Vilela:** Writing – review & editing, Visualization. **Bruna Araújo:** Writing – review & editing, Visualization. **Fábio G. Teixeira:** Writing – review & editing, Validation, Supervision, Project administration, Funding acquisition. **Inês Alencastre:** Writing – review & editing, Visualization, Validation, Supervision. **Inês Falcão Pires:** Writing – review & editing, Visualization, Validation, Supervision. **Carla Soares-Guedes:** Writing – review & editing, Visualization, Formal analysis. **Eduardo Gomes:** Writing – review & editing, Visualization, Formal analysis. **Joana Martins-Macedo:** Writing – review & editing, Visualization, Formal analysis. **Catarina Teixeira:** Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Rita Caridade-Silva:** Writing – review & editing, Visualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgments

The present work was supported by Prémios Santa Casa Neurociências-Prize Mantero Belard for Neurodegenerative Diseases Research (MB-28-2019) by Santa Casa da Misericórdia de Lisboa, and the Portuguese Foundation for Science and Technology (FCT) to Fábio Teixeira (2021.00643.CEECIND), Catarina Teixeira (2022.12641.BD), Bruna Araújo (2022.13292.BD), Carla Guedes (2023.03466.BD), Rita Silva (2022.13323.BD), and Joana Macedo (2023.00893.BDANA). The authors acknowledge BioRender for providing the illustrations used to create the figures in this manuscript.

## References

Abiodun, O.A., Ola, M.S., 2020. Role of brain renin angiotensin system in neurodegeneration: an update. Saudi J. Biol. Sci. 27 (3), 905–912. https://doi.org/10.1016/j.sjbs.2020.01.026.

Acharya, S., Salgado-somoza, A., Stefanizzi, F.M., Lumley, A.I., Zhang, L., Glaab, E., May, P., Devaux, Y., 2020. Non-coding RNAs in the brain-heart axis. Case Park. ' S. Dis.

Adesso, S., Magnus, T., Cuzzocrea, S., Campolo, M., Rissiek, B., Paciello, O., Autore, G., Pinto, A., Marzocco, S., 2017. Indoxyl sulfate affects glial function increasing oxidative stress and neuroinflammation in chronic kidney disease: interaction between astrocytes and microglia. Front. Pharmacol. 8 (JUN), 1–13. https://doi.org/10.3389/fphar.2017.00370.

Alves, M., Caldeira, D., Ferro, J.M., Ferreira, J.J., 2020. Does Parkinson's disease increase the risk of cardiovascular events? A systematic review and meta-analysis. Eur. J. Neurol. 27 (2), 288–296. https://doi.org/10.1111/ene.14076.

Ames, M.K., Atkins, C.E., Pitt, B., 2019. The renin-angiotensin-aldosterone system and its suppression. J. Vet. Intern. Med. 33 (2), 363–382. https://doi.org/10.1111/jvim.15454.

Andersson, J., 2005. The inflammatory reflex - introduction. J. Intern. Med. 257 (2), 122–125. https://doi.org/10.1111/j.1365-2796.2004.01440.x.

Angelova, P.R.; Ludtmann, M.H.R.; Horrocks, M.H.; Negoda, A. Calcium Is a Key Factor in α -Synuclein Induced Neurotoxicity. 2016, No. March.

Araque, A., Carmignoto, G., Haydon, P.G., Oliet, S.H.R., Robitaille, R., Volterra, A., 2014. Gliotransmitters travel in time and space. Neuron 81 (4), 728–739. https://doi.org/10.1016/j.neuron.2014.02.007.

Assem, M., Lando, M., Grissi, M., Kamel, S., Massy, Z.A., Chillon, J.M., Hénaut, L., 2018. The impact of uremic toxins on cerebrovascular and cognitive disorders. Toxins 10 (7), 1–25. https://doi.org/10.3390/toxins10070303.

Augustine, G.J., Santamaria, F., Tanaka, K., Carolina, N., 2003. Augustine 03NRN Local Ca Review. Pdf. Neuron 40, 331–346.

Baba, Y., Higuchi, M.A., Fukuyama, K., Abe, H., Uehara, Y., Inoue, T., Yamada, T., 2011. Effect of chronic kidney disease on excessive daytime sleepiness in Parkinson disease. Eur. J. Neurol. 18 (11), 1299–1303. https://doi.org/10.1111/j.1468-1331.2011.03391.x.

Baek, S.H., Park, S., Yu, M. yeon, Kim, J.E., Park, S.H., Han, K., Kim, Y.C., Kim, D.K., Joo, K.W., Kim, Y.S., Lee, H., 2021. Incident Parkinson's disease in kidney transplantation recipients: a nationwide population-based cohort study in Korea. Sci. Rep. 11 (1), 1–8. https://doi.org/10.1038/s41598-021-90130-9.

Benarroch, E.E., 1993. The central autonomic network: functional organization, dysfunction, and perspective. Mayo Clin. Proc. 68 (10), 988–1001. https://doi.org/10.1016/S0025-6196(12)62272-1.

Berg, D., Borghammer, P., Fereshtehnejad, S.M., Heinzel, S., Horsager, J., Schaeffer, E., Postuma, R.B., 2021. Prodromal Parkinson disease subtypes — key to understanding heterogeneity. Nat. Rev. Neurol. 17 (6), 349–361. https://doi.org/10.1038/s41582-021-00486-9.

Bhatia, D.; Choi, M.E. Autophagy in Kidney Disease: Advances and Therapeutic Potential, 1st ed.; Elsevier Inc., 2020; Vol. 172. https://doi.org/10.1016/bs.pmbts.2020.01.008.

Block, G., Port, F.K., 2003. Calcium phosphate metabolism and cardiovascular disease in patients with chronic kidney disease. Semin. Dial. 16 (2), 140–147. https://doi.org/10.1046/j.1525-139X.2003.160301.x.

Bloem, B.R., Okun, M.S., Klein, C., 2021. Parkinson's disease. Lancet 397 (10291), 2284–2303. https://doi.org/10.1016/S0140-6736(21)00218-X.

Bossola, M., Picconi, B., 2024. Uremic toxins and the brain in chronic kidney disease. J. Nephrol. 37 (5), 1391–1395. https://doi.org/10.1007/s40620-024-01929-4.

Braak, H.; Del, K.; Rüb, U.; Vos, R.A. I.De; Jansen, E.N. H.; Braak, E. Staging of Brain Pathology Related to Sporadic Parkinson ' s Disease. 2003b, 24, 197–211.

Braak, H., Rüb, U., Gai, W.P., Del Tredici, K., 2003a. Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J. Neural Transm. 110 (5), 517–536. https://doi.org/10.1007/s00702-002-0808-2.

Brokowski, C., A.M., 2019. 乳鼠心肌提取 HHS public access. Physiol. Behav. 176 (5), 139–148. https://doi.org/10.1002/ana.25564.Associations.

Bucolo, C., Leggio, G.M., Drago, F., Salomone, S., 2019. Dopamine outside the brain: the eye, cardiovascular system and endocrine pancreas. Pharmacol. Ther. 203, 107392. https://doi.org/10.1016/j.pharmthera.2019.07.003.

Van Den Buuse, M., 1997. Pressor responses to brain dopaminergic stimulation. Clin. Exp. Pharmacol. Physiol. 24 (9–10), 764–769. https://doi.org/10.1111/j.1440-1681.1997.tb02129.x.

Byku, M., Mann, D.L., 2016. Neuromodulation of the Failing Heart. Elsevier Inc. https://doi.org/10.1016/B978-0-12-800040-3.00019-4

Cersosimo, M.G.; Benarroch, E.E. Central Control of Autonomic Function and Involvement in Neurodegenerative Disorders, 1st ed.; Elsevier B.V., 2013; Vol. 117. https://doi.org/10.1016/B978-0-444-53491-0.00005-5.

Chandran, R., Kumar, M., Kesavan, L., Jacob, R.S., Gunasekaran, S., Lakshmi, S., Sadasivan, C., Omkumar, R.V., 2019. Cellular Calcium Signaling in the Aging Brain. J. Chem. Neuroanat. 95 (ember 2017), 95–114. https://doi.org/10.1016/j.jchemneu.2017.11.008.

Chan, C.S., Guzman, J.N., Ilijic, E., Mercer, J.N., Rick, C., Tkatch, T., Meredith, G.E., Surmeier, D.J., 2007. Rejuvenation" protects neurons in mouse models of Parkinson's disease. Nature 447 (7148), 1081–1086. https://doi.org/10.1038/nature05865.

Choi, M.R., 2015. Renal dopaminergic system: pathophysiological implications and clinical perspectives. World J. Nephrol. 4 (2), 196. https://doi.org/10.5527/wjn.v4.i2.196.

Clapham, D.E., 2007. Calcium signaling. Cell 131 (6), 1047–1058. https://doi.org/10.1016/j.cell.2007.11.028.

Cosarderelioglu, C., Nidadavolu, L.S., George, C.J., Oh, E.S., Bennett, D.A., Walston, J.D., Abadir, P.M., 2020. Brain renin–angiotensin system at the intersect of physical and cognitive frailty. Front. Neurosci. 14 (September), 1–29. https://doi.org/10.3389/fnins.2020.586314.

Cosselman, K.E., Navas-Acien, A., Kaufman, J.D., 2015. Environmental factors in cardiovascular disease. Nat. Rev. Cardiol. 12 (11), 627–642. https://doi.org/10.1038/nrcardio.2015.152.

Cuenca-Bermejo, L., Almela, P., Navarro-Zaragoza, J., Villalba, E.F., González-Cuello, A. M., Laorden, M.L., Herrero, M.T., 2021. Cardiac changes in Parkinson's disease: lessons from clinical and experimental evidence. Int. J. Mol. Sci. 22 (24). https://doi.org/10.3390/ijms222413488.

Ding, K., Tarumi, T., Wang, C., Vernino, S., Zhang, R., Zhu, D.C., 2020. Central autonomic network functional connectivity: correlation with baroreflex function and cardiovascular variability in older adults. Brain Struct. Funct. 225 (5), 1575–1585. https://doi.org/10.1007/s00429-020-02075-w.

Doggrell, S.A., 2002. The therapeutic potential of dopamine modulators on the cardiovascular and renal systems. Expert Opin. Investig. Drugs 11 (5), 631–644. https://doi.org/10.1517/13543784.11.5.631.

Eisner, D.A., Caldwell, J.L., Trafford, A.W., Hutchings, D.C., 2020. The control of diastolic calcium in the heart: basic mechanisms and functional implications. Circ. Res. 395–412. https://doi.org/10.1161/CIRCRESAHA.119.315891.

Eisner, D., 2014. Calcium in the heart: from physiology to disease. Exp. Physiol. 99 (10), 1273–1282. https://doi.org/10.1113/expphysiol.2013.077305.

Elliott, W.J., Ram, C.V.S., 2011. Calcium channel blockers. J. Clin. Hypertens. 13 (9), 687–689. https://doi.org/10.1111/j.1751-7176.2011.00513.x.

Endo, M., 1977. Calcium release from the sarcoplasmic reticulum. Physiol. Rev. 57 (1), 71–108. https://doi.org/10.1152/physrev.1977.57.1.71.

Foley, R.N., Parfrey, P.S., Harnett, J.D., Kent, G.M., Hu, L., O'Dea, R., Murray, D.C., B. P, 1996. Hypocalcemia, morbidity, and mortality in end-stage renal disease. Am. J. Nephrol. 16 (5), 386–393.

Fornai, F., Ruffoli, R., Soldani, P., Ruggieri, S., Paparelli, A., 2007. The "Parkinsonian Heart": from novel vistas to advanced therapeutic approaches in Parkinsons disease. Curr. Med. Chem. 14 (23), 2421–2428. https://doi.org/10.2174/092986707782023631.

Frishman, W.H., 2007. Calcium channel blockers: differences between subclasses. Am. J. Cardiovasc. Drugs 7 (. 1), 17–23. https://doi.org/10.2165/00129784-200707010-00002.

Gallo, G., Lanza, O., Savoia, C., 2023. New insight in cardiorenal syndrome: from biomarkers to therapy. Int. J. Mol. Sci. 24 (6), 5089. https://doi.org/10.3390/ijms24065089.

Greenland, J.C., Williams-Gray, C.H., Barker, R.A., 2019. The clinical heterogeneity of Parkinson's disease and its therapeutic implications. Eur. J. Neurosci. 49 (3), 328–338. https://doi.org/10.1111/ejn.14094.

Günaydın, Z.Y., Bektaş, O., Karagöz, A., Özer, F.F., 2016. Effects of levodopa therapy on global left ventricular systolic function in patients with Parkinson disease. Wien. Klin. Wochenschr. 128 (13–14), 528–533. https://doi.org/10.1007/s00508-016-1026-5.

Guzman, J.N., Sánchez-Padilla, J., Chan, C.S., Surmeier, D.J., 2009. Robust pacemaking in substantia Nigra dopaminergic neurons. J. Neurosci. 29 (35), 11011–11019. https://doi.org/10.1523/JNEUROSCI.2519-09.2009.

Hamed, S.A., 2019. Neurologic conditions and disorders of uremic syndrome of chronic kidney disease: presentations, causes, and treatment strategies. Expert Rev. Clin. Pharmacol. 12 (1), 61–90. https://doi.org/10.1080/17512433.2019.1555468.

Hampton, J.R., van Veldhuisen, D.J., Kleber, F.X., Cowley, A.J., Ardia, A., Block, P., Cortina, A., Cserhalmi, L., Follath, F., Jensen, G., Kayanakis, J., Lie, K.I., Mancia, G., Skene, A.M., 1997. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. second prospective randomised study of ibopamine on mortality and efficacy (PRIME II) investigators. Lancet 349 (9057), 971–977.

Hanna, R.M., Ahdoot, R.S., Kalantar-Zadeh, K., Ghobry, L., Kurtz, I., 2022. Calcium transport in the kidney and disease processes. Front. Endocrinol. (Lausanne). 12 (March), 1–11. https://doi.org/10.3389/fendo.2021.762130.

Henein, M.Y., Vancheri, S., Longo, G., Vancheri, F., 2022. The role of inflammation in cardiovascular disease. Int. J. Mol. Sci. 23 (21). https://doi.org/10.3390/ijms232112906.

Hiemstra, B., Koster, G., Wetterslev, J., Gluud, C., Jakobsen, J.C., Scheeren, T.W.L., Keus, F., van der Horst, I.C.C., 2019. Dopamine in critically Ill patients with cardiac dysfunction: a systematic review with meta-analysis and trial sequential analysis. Acta Anaesthesiol. Scand. 63 (4), 424–437. https://doi.org/10.1111/aas.13294.

Hill Gallant, K.M., Spiegel, D.M., 2017. Calcium balance in chronic kidney disease. Curr. Osteoporos. Rep. 15 (3), 214–221. https://doi.org/10.1007/s11914-017-0368-x.

Hong, C.T., Chan, L., Wu, D., Chen, W.T., Chien, L.N., 2019. Association between Parkinson's disease and atrial fibrillation: a population-based study. Front. Neurol. 10 (FEB). https://doi.org/10.3389/fneur.2019.00022.

Hou, L., Li, Q., Jiang, L., Qiu, H., Geng, C., Hong, J.S., Li, H., Wang, Q., 2018. Hypertension and diagnosis of Parkinson's disease: a meta-analysis of cohort studies. Front. Neurol. 9 (MAR), 1–9. https://doi.org/10.3389/fneur.2018.00162.

Huang, Y., Ren, H., Gao, X., Cai, D., Shan, H., Bai, J., Sheng, L., Jin, Y., Zhou, X., 2022. Amlodipine improves spinal cord injury repair by inhibiting motoneuronal apoptosis through autophagy upregulation. Spine (Phila. Pa. 1976). 47 (17), E570–E578. https://doi.org/10.1097/BRS.0000000000004310.

Iniguez, M., Jimenez-Marin, A., Erramuzpe, A., Acera, M., Tijero, B., Murueta-Goyena, A., Del Pino, R., Fernandez, T., Carmona-Abellan, M., Cabrera-Zubizarreta, A., Gómez-Esteban, J.C., Cortes, J.M., Gabilondo, I., 2022. Heart-brain synchronization breakdown in Parkinson's disease. npj Park. Dis. 8 (1), 1–11. https://doi.org/10.1038/s41531-022-00323-w.

Jackson, L., Eldahshan, W., Fagan, S.C., Ergul, A., 2018. Within the brain: the renin angiotensin system. Int. J. Mol. Sci. 19 (3), 1–23. https://doi.org/10.3390/ijms19030876.

Jain, S., Goldstein, D.S., 2012. Cardiovascular dysautonomia in Parkinson disease: from pathophysiology to pathogenesis. Neurobiol. Dis. 46 (3), 572–580. https://doi.org/10.1016/j.nbd.2011.10.025.

James Surmeier, D., Guzman, J.N., Sanchez, J., Schumacker, P.T., 2012. Physiological phenotype and vulnerability in Parkinson's disease. Cold Spring Harb. Perspect. Med. 2 (7), 1–27. https://doi.org/10.1101/cshperspect.a009290.

Jankowski, J., Floege, J., Fliser, D., Böhm, M., Marx, N., 2021. Cardiovascular disease in chronic kidney disease: pathophysiological insights and therapeutic options. Circulation 1157–1172. https://doi.org/10.1161/CIRCULATIONAHA.120.050686.

Janmaat, C.J., Van Diepen, M., Gasparini, A., Evans, M., Qureshi, A.R., Ärnlöv, J., Barany, P., Elinder, C.G., Rotmans, J.I., Vervloet, M., Dekker, F.W., Carrero, J.J., 2018. Lower serum calcium is independently associated with CKD progression. Sci. Rep. 8 (1), 1–9. https://doi.org/10.1038/s41598-018-23500-5.

Junho, C.V.C., Trentin-Sonoda, M., Panico, K., dos Santos, R.S.N., Abrahão, M.V., Vernier, I.C.S., Fürstenau, C.R., Carneiro-Ramos, M.S., 2022. Cardiorenal syndrome: long road between kidney and heart. Heart Fail. Rev. 27 (6), 2137–2153. https://doi.org/10.1007/s10741-022-10218-w.

Kalia, L.V., Lang, A.E., 2015. Parkinson's disease. Lancet 386 (9996), 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3.

Kayed, R., Sokolov, Y., Edmonds, B., McIntire, T.M., Milton, S.C., Hall, J.E., Glabe, C.G., 2004. Permeabilization of lipid bilayers is a common conformation-dependent activity of soluble amyloid oligomers in protein misfolding diseases. J. Biol. Chem. 279 (45), 46363–46366. https://doi.org/10.1074/jbc.C400260200.

Kelly, P.J., Lemmens, R., Tsivgoulis, G., 2021. Inflammation and stroke risk: a new target for prevention. Stroke 52 (8), 2697–2706. https://doi.org/10.1161/STROKEAHA.121.034388.

Ke, L., Zhao, L., Xing, W., Tang, Q., 2024. Association between Parkinson's disease and cardiovascular disease mortality: a prospective population-based study from NHANES. Lipids Health Dis. 23 (1), 1–10. https://doi.org/10.1186/s12944-024-02200-2.

Kim, J., Pajarillo, E., Rizor, A., Son, D.S., Lee, J., Aschner, M., Lee, E., 2019. LRRK2 kinase plays a critical role in manganese-induced inflammation and apoptosis in microglia. PLoS One 14 (1), 1–23. https://doi.org/10.1371/journal.pone.0210248.

Kim, D.K., 2024. Mid- and late-life chronic kidney disease is associated with Parkinson's disease, not with an increased risk of Alzheimer's disease. J. Pers. Med. 14 (6). https://doi.org/10.3390/jpm14060597.

Kitagawa, T., Umehara, T., Oka, H., Shiraishi, T., Sato, T., Takatsu, H., Nakahara, A., Matsuno, H., Bono, K., Omoto, S., Murakami, H., Sengoku, R., Iguchi, Y., 2021. Association between heart rate variability and striatal dopamine depletion in Parkinson's Disease. J. Neural Transm. 128 (12), 1835–1840. https://doi.org/10.1007/s00702-021-02418-9.

Köttgen, A., Cornec-Le Gall, E., Halbritter, J., Kiryluk, K., Mallett, A.J., Parekh, R.S., Rasouly, H.M., Sampson, M.G., Tin, A., Antignac, C., Ars, E., Bergmann, C., Bleyer, A.J., Bockenhauer, D., Devuyst, O., Florez, J.C., Fowler, K.J., Franceschini, N., Fukagawa, M., Gale, D.P., Gbadegesin, R.A., Goldstein, D.B., Grams, M.E., Greka, A., Gross, O., Guay-Woodford, L.M., Harris, P.C., Hoefele, J., Hung, A.M., Knoers, N.V.A.M., Kopp, J.B., Kretzler, M., Lanktree, M.B., Lipska-Ziętkiewicz, B.S., Nicholls, K., Nozu, K., Ojo, A., Parsa, A., Pattaro, C., Pei, Y., Pollak, M.R., Rhee, E.P., Sanna-Cherchi, S., Savige, J., Sayer, J.A., Scolari, F., Sedor, J.R., Sim, X., Somlo, S., Susztak, K., Tayo, B.O., Torra, R., van Eerde, A.M., Weinstock, A., Winkler, C.A., Wuttke, M., Zhang, H., King, J.M., Cheung, M., Jadoul, M., Winkelmayer, W.C., Gharavi, A.G., 2022. Genetics in CHronic Kidney Disease: Conclusions from A Kidney Disease: Improving global outcomes (KDIGO) controversies conference. Kidney Int 101 (6), 1126–1141. https://doi.org/10.1016/j.kint.2022.03.019.

Lavandero, S., Chiong, M., Rothermel, B.A., Hill, J.A., 2015. Autophagy in cardiovascular biology. J. Clin. Invest. 125 (1), 55–64. https://doi.org/10.1172/JCI73943.

Leszek, J., Mikhaylenko, E.V., Belousov, D.M., Koutsouraki, E., Szczechowiak, K., Kobusiak-Prokopowicz, M., Mysiak, A., Diniz, B.S., Somasundaram, S.G., Kirkland, C.E., Aliev, G., 2020. The links between cardiovascular diseases and Alzheimer's disease. Curr. Neuropharmacol. 19 (2), 152–169. https://doi.org/10.2174/1570159x18666200729093724.

Lewandowski, M.J., Krenn, S., Kurnikowski, A., Bretschneider, P., Sattler, M., Schwaiger, E., Antlanger, M., Gauckler, P., Pirklbauer, M., Brunner, M., Horn, S., Zitt, E., Kirsch, B., Windpessl, M., Wallner, M., Aringer, I., Wiesholzer, M., Hecking, M., Hödlmoser, S., 2023. Chronic kidney disease is more prevalent among women but more men than women are under nephrological care: analysis from six outpatient clinics in Austria 2019. Wien. Klin. Wochenschr. 135 (3–4), 89–96. https://doi.org/10.1007/s00508-022-02074-3.

Liabeuf, S., Pepin, M., Franssen, C.F.M., Viggiano, D., Carriazo, S., Gansevoort, R.T., Gesualdo, L., Hafez, G., Malyszko, J., Mayer, C., Nitsch, D., Ortiz, A., Pešić, V., Wiecek, A., Massy, Z.A., 2021. Chronic kidney disease and neurological disorders: are uraemic toxins the missing piece of the Puzzle? Nephrol. Dial. Transpl. 37 (2), ii33–ii44. https://doi.org/10.1093/ndt/gfab223.

Lim, L.M., Kuo, H.T., Kuo, M.C., Chiu, Y.W., Lee, J.J., Hwang, S.J., Tsai, J.C., Hung, C.C., Chen, H.C., 2014. Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3-4 patients. BMC Nephrol. 15 (1), 1–9. https://doi.org/10.1186/1471-2369-15-183.

Loera-Valencia, R., Eroli, F., Garcia-Ptacek, S., Maioli, S., 2021. Brain renin–angiotensin system as novel and potential therapeutic target for Alzheimer's disease. Int. J. Mol. Sci. 22 (18). https://doi.org/10.3390/ijms221810139.

Ludtmann, M.H.R., Abramov, A.Y., 2018. Mitochondrial calcium imbalance in Parkinson's disease. Neurosci. Lett. 663 (August), 86–90. https://doi.org/10.1016/j.neulet.2017.08.044.

Mallappallil, M., Friedman, E.A., Delano, B.G., Mcfarlane, S.I., Salifu, M.O., 2014. Chronic kidney disease in the elderly: evaluation and management. Clin. Pract. 11 (5), 525–535. https://doi.org/10.2217/cpr.14.46.

Marina, N., Teschemacher, A.G., Kasparov, S., Gourine, A.V., 2016. Glia, sympathetic activity and cardiovascular disease. Exp. Physiol. 101 (5), 565–576. https://doi.org/10.1113/EP085713.

Marras, C., Gruneir, A., Rochon, P., Wang, X., Anderson, G., Brotchie, J., Bell, C.M., Fox, S., Austin, P.C., 2012. Dihydropyridine calcium channel blockers and the progression of parkinsonism. Ann. Neurol. 71 (3), 362–369. https://doi.org/10.1002/ana.22616.

Massel, D., Girbes, A.R.J., Zijlstra, J.G., Hampton, J.R., Van Veldhuisen, D., Kleber, F., 1997. Ibopamine and survival in severe congestive heart failure: PRIME II (Multiple Letters) [16]. Lancet 350 (9071), 147–148. https://doi.org/10.1016/s0140-6736(05)61857-0.

Matsubara, B.B., Franco, M., Janicki, J.S., Matsubara, L.S., 2010. Effect of felodipine on myocardial and renal injury induced by aldosterone-high salt hypertension in uninephrectomized rats. Braz. J. Med. Biol. Res. 43 (5), 506–514. https://doi.org/10.1590/S0100-879X2010007500037.

Ma, L.Y., Liu, G.L., Wang, D.X., Zhang, M.M., Kou, W.Y., Feng, T., 2019. Alpha-synuclein in peripheral tissues in Parkinson's disease. ACS Chem. Neurosci. https://doi.org/10.1021/acschemneuro.8b00383.

Meléndez-Flores, J.D., Estrada-Bellmann, I., 2021. Linking chronic kidney disease and Parkinson's disease: a literature review. Metab. Brain Dis. 36 (1), 1–12. https://doi.org/10.1007/s11011-020-00623-1.

Minciunescu, A., Genovese, L., deFilippi, C., 2022. Cardiovascular alterations and structural changes in the setting of chronic kidney disease: a review of cardiorenal syndrome type 4. SN Compr. Clin. Med. 5 (1). https://doi.org/10.1007/s42399-022-01347-2.

Moorthi, R.N., Moe, S.M., 2011. CK-dmineral and bone disorder: core curriculum 2011. Am. J. Kidney Dis. 58 (6), 1022–1036. https://doi.org/10.1053/j.ajkd.2011.08.009.

Mukherjee, U.A., Ong, S.B., Ong, S.G., Hausenloy, D.J., 2015. Parkinson's disease proteins: novel mitochondrial targets for cardioprotection. Pharmacol. Ther. 156, 34–43. https://doi.org/10.1016/j.pharmthera.2015.10.005.

Nakagawa, N., Fukawa, N., Tsuji, K., Nakano, N., Kato, A., 2016. Takotsubo cardiomyopathy induced by dopamine infusion after carotid artery stenting. Int. J. Cardiol. 205, 62–64. https://doi.org/10.1016/j.ijcard.2015.12.023.

Nam, G.E., Kim, N.H., Han, K., Choi, K.M., Chung, H.S., Kim, J.W., Han, B., Cho, S.J., Jung, S.J., Yu, J.H., Park, Y.G., Kim, S.M., 2019. Chronic renal dysfunction, proteinuria, and risk of Parkinson's disease in the elderly. Mov. Disord. 34 (8), 1184–1191. https://doi.org/10.1002/mds.27704.

Nechushtai, L., Frenkel, D., Pinkas-Kramarski, R., 2023. Autophagy in Parkinson's disease. Biomolecules 13 (10). https://doi.org/10.3390/biom13101435.

Neumann, J., Hofmann, B., Dhein, S., Gergs, U., 2023. Role of dopamine in the heart in health and disease. Int. J. Mol. Sci. 24 (5), 1–35. https://doi.org/10.3390/ijms24055042.

Nishida, K., Kyoi, S., Yamaguchi, O., Sadoshima, J., Otsu, K., 2009. The role of autophagy in the heart. Cell Death Differ. 16 (1), 31–38. https://doi.org/10.1038/cdd.2008.163.

Noack, C., Schroeder, C., Heusser, K., Lipp, A., 2014. Cardiovascular effects of levodopa in Parkinson's disease. Park. Relat. Disord. 20 (8), 815–818. https://doi.org/10.1016/j.parkreldis.2014.04.007.

Ohno, S., Ishii, A., Yanagita, M., Yokoi, H., 2022. Calcium channel blocker in patients with chronic kidney disease. Clin. Exp. Nephrol. 26 (3), 207–215. https://doi.org/10.1007/s10157-021-02153-1.

Oka, H., Toyoda, C., Yogo, M., Mochio, S., 2010. Olfactory dysfunction and cardiovascular dysautonomia in Parkinson's disease. J. Neurol. 257 (6), 969–976. https://doi.org/10.1007/s00415-009-5447-1.

Osborn, J.W., Foss, J.D., 2017. Renal nerves and long-term control of arterial pressure. Compr. Physiol. 7 (2), 263–320. https://doi.org/10.1002/cphy.c150047.
O'Neill, W.C., 2016. Targeting serum calcium in chronic kidney disease and end-stage renal disease: is normal too high? Kidney Int 89 (1), 40–45. https://doi.org/10.1016/j.kint.2015.10.001.
Palmer, S.C., Hayen, A., Macaskill, P., Pellegrini, F., Craig, J.C., Elder, G.J., Strippoli, G. F., 2011. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death in individuals with chronic kidney disease. JAMA 305 (11), 1119–1127.
Pchitskaya, E., Popugaeva, E., Bezprozvanny, I., 2018. Calcium signaling and molecular mechanisms underlying neurodegenerative diseases. Cell Calcium 70, 87–94. https://doi.org/10.1016/j.ceca.2017.06.008.
Pelliccia, F., Kaski, J.C., Crea, F., Camici, P.G., 2017. Pathophysiology of Takotsubo Syndrome. Circulation 135 (24), 2426–2441. https://doi.org/10.1161/CIRCULATIONAHA.116.027121.
Peng, H., Wu, L., Chen, Q., Chen, S., Wu, S., Shi, X., Ma, J., Yang, H., Li, X., 2024. Association between kidney function and Parkinson's disease risk: a prospective study from the UK biobank. BMC Public Health 24 (1). https://doi.org/10.1186/s12889-024-19709-x.
Perrone, L., Valente, M., 2021. The emerging role of metabolism in brain-heart axis: new challenge for the therapy and prevention of Alzheimer Disease: may thioredoxin interacting protein (Txnip) play a role? Biomolecules 11 (11). https://doi.org/10.3390/biom11111652.
Piqueras-Flores, J., López-García, A., Moreno-Reig, Á., González-Martínez, A., Hernández-González, A., Vaamonde-Gamo, J., Jurado-Román, A., 2018. Structural and functional alterations of the heart in Parkinson's disease. Neurol. Res. 40 (1), 53–61. https://doi.org/10.1080/01616412.2017.1390933.
Pliquett, R.U., 2022. Cardiorenal syndrome: an updated classification based on clinical hallmarks. J. Clin. Med. 11 (10). https://doi.org/10.3390/jcm11102896.
Puopolo, M., Raviola, E., Bean, B.P., 2007. Roles of subthreshold calcium current and sodium current in spontaneous firing of mouse midbrain dopamine neurons. J. Neurosci. 27 (3), 645–656. https://doi.org/10.1523/JNEUROSCI.4341-06.2007.
Qaddumi, W.N., Jose, P.A., 2021. The role of the renal dopaminergic system and oxidative stress in the pathogenesis of hypertension. Biomedicines 9 (2), 1–24. https://doi.org/10.3390/biomedicines9020139.
Quiroga, B., Ortiz, A., Navarro-González, J.F., Santamaría, R., de Sequera, P., Díez, J., 2023. From cardiorenal syndromes to cardionephrology: a reflection by nephrologists on renocardiac syndromes. Clin. Kidney J. 16 (1), 19–29. https://doi.org/10.1093/ckj/sfac113.
Qu, Y., Qin, Q.X., Wang, D.L., Li, J.T., Zhao, J.W., An, K., Li, J.Y., Mao, Z.J., Min, Z., Xiong, Y.J., Xue, Z., 2023. Estimated glomerular filtration rate is a biomarker of cognitive impairment in Parkinson's disease. Front. Aging Neurosci. 15 (May). https://doi.org/10.3389/fnagi.2023.1130833.
Rai, N.K., Wang, Z., Drawz, P.E., Connett, J., Murphy, D.P., 2023. CKD progression risk and subsequent cause of death: a population-based cohort study. Kidney Med 5 (4), 100604. https://doi.org/10.1016/j.xkme.2023.100604.
Rangaswami, J.; Bhalla, V.; Blair, J.E.A.; Chang, T.I.; Costa, S.; Lentine, K.L.; Lerma, E.V.; Mezue, K.; Molitch, M.; Mullens, W.; Ronco, C.; Tang, W.H.W.; Mccullough, P.A. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association; 2019; Vol. 139. https://doi.org/10.1161/CIR.0000000000000664.
Reich, S.G., Savitt, J.M., 2019. Parkinson's disease. Med. Clin. North Am. 103 (2), 337–350. https://doi.org/10.1016/j.mcna.2018.10.014.
Rodgers, J.L., Jones, J., Bolleddu, S.I., Vanthenapalli, S., Rodgers, L.E., Shah, K., Karia, K., Panguluri, S.K., 2019. Cardiovascular risks associated with gender and aging. J. Cardiovasc. Dev. Dis. 6 (2). https://doi.org/10.3390/jcdd6020019.
Ronco, C., Bellasi, A., Di Lullo, L., 2018. Cardiorenal syndrome: an overview. Adv. Chronic Kidney Dis. 25 (5), 382–390. https://doi.org/10.1053/j.ackd.2018.08.004.
Ronco, C., Haapio, M., House, A.A., Anavekar, N., Bellomo, R., 2008. Cardiorenal syndrome. J. Am. Coll. Cardiol. 52 (19), 1527–1539. https://doi.org/10.1016/j.jacc.2008.07.051.
Ruby, M., Gifford, C.C., Pandey, R.P., Raj, V.S., Sabbisetti, V.S., Ajay, A.K., 2023. Autophagy as a therapeutic target for chronic kidney disease and the roles of TGF-B1 in autophagy and kidney fibrosis. Cells 12 (3), 1–17. https://doi.org/10.3390/cells12030412.
Safarpour, Y., Vaziri, N.D., Jabbari, B., 2021. Movement disorders in chronic kidney disease – a descriptive review. J. Stroke Cerebrovasc. Dis. 30 (9), 105408. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105408.
Schwarz, S., Trivedi, B.K., Kalantar-Zadeh, K., Kovesdy, C.P., 2006. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin. J. Am. Soc. Nephrol. 1 (4), 825–831. https://doi.org/10.2215/CJN.02101205.
Scorza, F.A., Fiorini, A.C., Scorza, C.A., Finsterer, J., 2018. Cardiac abnormalities in Parkinson's disease and parkinsonism. J. Clin. Neurosci. 53, 1–5. https://doi.org/10.1016/j.jocn.2018.04.031.
Shah, K., Seeley, S., Schulz, C., Fisher, J., Rao, S.G., 2022. Calcium channels in the heart: disease states and drugs. Cells 11 (6), 1–11. https://doi.org/10.3390/cells11060943.
Shanahan, C.M., Crouthamel, M.H., Kapustin, A., Giachelli, C.M., 2011. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. Circ. Res. 109 (6), 697–711. https://doi.org/10.1161/CIRCRESAHA.110.234914.
Sharabi, Y., Vatine, G.D., Ashkenazi, A., 2021. Parkinson's disease outside the brain: targeting the autonomic nervous system. Lancet Neurol. 20 (10), 868–876. https://doi.org/10.1016/S1474-4422(21)00219-2.
Siddiqi, F.H., Menzies, F.M., Lopez, A., Stamatakou, E., Karabiyik, C., Ureshino, R., Ricketts, T., Jimenez-Sanchez, M., Esteban, M.A., Lai, L., Tortorella, M.D., Luo, Z., Liu, H., Metzakopian, E., Fernandes, H.J.R., Bassett, A., Karran, E., Miller, B.L., Fleming, A., Rubinsztein, D.C., 2019. Felodipine induces autophagy in mouse brains with pharmacokinetics amenable to repurposing. Nat. Commun. 10 (1), 1–14. https://doi.org/10.1038/s41467-019-09494-2.
Silva, A.S., Ariza, D., Dias, D.P.M., Crestani, C.C., Martins-Pinge, M.C., 2015. Cardiovascular and autonomic alterations in rats with parkinsonism induced by 6-OHDA and treated with L-DOPA. Life Sci. 127, 82–89. https://doi.org/10.1016/j.lfs.2015.01.032.
Song, J., Kim, J., 2016. Degeneration of dopaminergic neurons due to metabolic alterations and Parkinson's disease. Front. Aging Neurosci. 8 (MAR), 1–11. https://doi.org/10.3389/fnagi.2016.00065.
Song, R., Pan, K.Y., Xu, H., Qi, X., Buchman, A.S., Bennett, D.A., Xu, W., 2021. Association of cardiovascular risk burden with risk of dementia and brain pathologies: a population-based cohort study. Alzheimer'S. Dement 17 (12), 1914–1922. https://doi.org/10.1002/alz.12343.
Suman, S., Pravalika, J., Manjula, P., Farooq, U., 2023. Gender and CVD- Does It Really Matters? Curr. Probl. Cardiol. 48 (5), 101604. https://doi.org/10.1016/j.cpcardiol.2023.101604.
Surmeier, D.J., Schumacker, P.T., 2013. Calcium, bioenergetics, and neuronal vulnerability in Parkinson's disease. J. Biol. Chem. 288 (15), 10736–10741. https://doi.org/10.1074/jbc.R112.410530.
Surmeier, D.J., Schumacker, P.T., Guzman, J.D., Ilijic, E., Yang, B., Zampese, E., 2017. Calcium and Parkinson's disease. Biochem. Biophys. Res. Commun. 483 (4), 1013–1019. https://doi.org/10.1016/j.bbrc.2016.08.168.
Tedoldi, A., Argent, L., Montgomery, J.M., 2021. The role of the tripartite synapse in the heart: how glial cells may contribute to the physiology and pathophysiology of the intracardiac nervous system. Am. J. Physiol. - Cell Physiol. 320 (1), C1–C14. https://doi.org/10.1152/AJPCELL.00363.2020.
Titova, N., Padmakumar, C., Lewis, S.J.G., Chaudhuri, K.R., 2017. Parkinson's: a syndrome rather than a disease? J. Neural Transm. 124 (8), 907–914. https://doi.org/10.1007/s00702-016-1667-6.
Tsai, H.J., Wu, P.Y., Huang, J.C., Chen, S.C., 2021. Environmental pollution and chronic kidney disease. Int. J. Med. Sci. 18 (5), 1121–1129. https://doi.org/10.7150/ijms.51594.
Uduman, J., 2018. Epidemiology of cardiorenal syndrome. Adv. Chronic Kidney Dis. 25 (5), 391–399. https://doi.org/10.1053/j.ackd.2018.08.009.
Vaarmann, A., Gandhi, S., Gourine, A.V., Abramov, A.Y., 2010. Novel pathway for an old neurotransmitter: dopamine-induced neuronal calcium signalling via receptor-independent mechanisms. Cell Calcium 48 (2–3), 176–182. https://doi.org/10.1016/j.ceca.2010.08.008.
Venda, L.L., Cragg, S.J., Buchman, V.L., Wade-Martins, R., 2010. α-Synuclein and dopamine at the crossroads of Parkinson's disease. Trends Neurosci. 33 (12), 559–568. https://doi.org/10.1016/j.tins.2010.09.004.
Vizziello, M., Borellini, L., Franco, G., Ardolino, G., 2021. Disruption of mitochondrial homeostasis: the role of pink1 in Parkinson's disease. Cells 10 (11), 1–19. https://doi.org/10.3390/cells10113022.
Vrablik, M., Dlouha, D., Todorovova, V., Stefler, D., Hubacek, J.A., 2021. Genetics of cardiovascular disease: how far are we from personalized Cvd risk prediction and management? Int. J. Mol. Sci. 22 (8). https://doi.org/10.3390/ijms22084182.
Wakabayashi, K. Where and How Alpha-Synuclein Pathology Spreads in Parkinson ' s Disease: 2020, No. August, 415–425. https://doi.org/10.1111/neup.12691.
van Weperen, V.Y.H., Ripplinger, C.M., Vaseghi, M., 2023. Autonomic control of ventricular function in health and disease: current state of the art. Clin. Auton. Res. https://doi.org/10.1007/s10286-023-00948-8.
Yamaguchi, T., Sumida, T.S., Nomura, S., Satoh, M., Higo, T., Ito, M., Ko, T., Fujita, K., Sweet, M.E., Sanbe, A., Yoshimi, K., Manabe, I., Sasaoka, T., Taylor, M.R.G., Toko, H., Takimoto, E., Naito, A.T., Komuro, I., 2020. Cardiac dopamine D1 receptor triggers ventricular arrhythmia in chronic heart failure. Nat. Commun. 11 (1). https://doi.org/10.1038/s41467-020-18128-x.
Yao, L., Ye, Y., Mao, H., Lu, F., He, X., Lu, G., Zhang, S., 2018. MicroRNA-124 regulates the expression of MEKK3 in the inflammatory pathogenesis of Parkinson's disease. J. Neuroinflamm. 15 (1), 1–19. https://doi.org/10.1186/s12974-018-1053-4.
Yeh, T.L., Yang, Y.K., Chiu, N.T., Yao, W.J., Yeh, S.J., Wu, J.S., Chuang, J.I., Chang, S.H., 2006. Correlation between striatal dopamine D2/D3 receptor binding and cardiovascular activity in healthy subjects. Am. J. Hypertens. 19 (9), 964–969. https://doi.org/10.1016/j.amjhyper.2006.03.005.
Zakharov, S.D., Hulleman, J.D., Dutseva, E.A., Antonenko, Y.N., Rochet, J.C., Cramer, W. A., 2007. Helical α-synuclein forms highly conductive ion channels. Biochemistry 46 (50), 14369–14379. https://doi.org/10.1021/bi701275p.
Zhou, Y., Greka, A., 2016. Calcium-permeable ion channels in the kidney. Am. J. Physiol. - Ren. Physiol. 310 (11), F1157–F1167. https://doi.org/10.1152/ajprenal.00117.2016.
Zhou, Z., Zhang, M., Fang, Q., Huang, J., 2023. Relationship between Parkinson's disease and cardio-cerebrovascular diseases: a mendelian randomized study. Sci. Rep. 13 (1), 1–10. https://doi.org/10.1038/s41598-023-47708-2.
Zhu, R., Luo, Y., Li, S., Wang, Z., 2022. The role of microglial autophagy in Parkinson's disease. Front. Aging Neurosci. 14 (ember). https://doi.org/10.3389/fnagi.2022.1039780.