Exploring the Link Between Dopamine and Parkinson's Disease

Efe Yilmaz *

October 6, 2024

Abstract

The review claims that there is a relationship between dopamine and Parkinson's disease. Parkinson's disease is a progressive neurological disorder that results in the loss of motor and non-motor functions due to neurodegeneration in different parts of the brain. It is important to understand the key molecular pathogenic mechanisms behind Parkinson's disease including alpha-synuclein misfolding, mitochondrial dysfunction, and oxidative stress in order to bring an insightful approach to the second most common neurological disease among the society. Other than that, in order to justify the motor and non-motor symptoms of the disease, understanding the role of dopamine as a chemical messenger that regulates some motor and non-motor functions of the brain is crucial. Herewith, the missing parts in the relationship between dopamine-producing neurons and Parkinson's disease will be unrevealed, and sustainable therapeutic approaches can be determined.

1 Introduction

In 1817, James Parkinson, a member of The Royal College of Surgeons of the era, provided one of the earliest comprehensive descriptions of what we now recognize as Parkinson's disease. He characterized it as, "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured," (Parkinson, 1817).

Even though it has been studied for over two centuries, the exact cause of Parkinson's disease remains not fully understood. The disease has never lost its actuality with ongoing current research due to its high incidence rate and significant impact on society. Being a chronic and progressive neurological disorder that restricts the individual's movement and consciousness in fact, Parkinson's disease is the second most common neurodegenerative disease. According to Joseph Jankovic, an American neurologist at Baylor College of Medicine,

*Advised by: Arij Daou of The University of Chicago

"Parkinson's disease is the fastest growing of [neurological disorders]" (Jankovic and Tan, 2020). Revealing the great incidence rate of this neurodegenerative disease, data taken from the Parkinson's Foundation website indicates that nearly 90,000 people are newly diagnosed with Parkinson's Disease in the US every year.

Comprehending the prevalence of the disease raises the question of "Who is at risk of being diagnosed with Parkinson's disease and why?" While factors like "age", "gender", "genetic background," and "environmental factors" contribute to the different frequencies of the disease observed in society, as discussed in an article published on Neuroepidemiology, the complex expressions of the disease prevent researchers from attributing its cause to a single factor (Hirsch et al., 2016).

At this very point, it becomes evident that none of the individual determinants, such as age or gender, are sufficient to uncover the underlying causes of Parkinson's disease. Instead, attention turns to a crucial chemical signaling molecule that plays a central role in nerve cell communication and is responsible for the coordinated movements: dopamine. Besides its several important functions in the body, dopamine controls both motor and non-motor functions of the brain. Motor functions involve muscle movement, while non-motor functions are associated with cognitive processes. Henk J. Groenewegen, a professor from the Department of Anatomy and Neurosciences at Amsterdam University, underlines the importance of dopamine levels for both motor and non-motor functions of the brain in his article, stating that "Low dopamine levels are, therefore, associated with a paucity of movements as well as with cognitive and emotional/motivational behavior" (Groenewegen, 2003).

Comparing the similar non-functionalities resulting from low dopamine levels and those observed in Parkinson's disease, it becomes evident that there may be a closer link between dopamine and Parkinson's disease than previously believed. This review paper will delve into this connection.

2 Dopamine-producing neurons and substantia nigra

The substantia nigra, a particular group of neurons in the midbrain part of the brain, is where dopamine is mostly produced. Even though there are several unlinked dopaminergic cell groups distributed throughout different parts of the brain, Shankar Chinta and Julie Andersen, researchers from the Buck Institute for Age Research, state in their article that "the most prominent dopaminergic cell group resides in the ventral part of mesencephalon, which contains approximately 90

If dopamine production is observed, it becomes evident that those dopamine-producing neurons undergo a series of biochemical processes. The initial step for these neurons is to uptake tyrosine from the bloodstream. Tyrosine, an amino acid that is supplemented by the body mainly through tyrosine-rich food, under-

scores the importance of diet in order to keep dopamine production in the brain constant. Once dopamine is up-taken into the neurons, an article written by professors at the University of Chile describes the two-step process: "Dopamine is synthesized from the amino acid tyrosine in two steps (...): hydroxylation of tyrosine to L-DOPA, and decarboxylation of L-DOPA to dopamine" (Segura-Aguilar et al., 2014). Recalling hydroxylation is a chemical process, in which the C-H bond is oxidized to the C-OH bond and results in the introduction of a new hydroxyl group to the compound, it can be understood that enzymatic activity in neurons is also crucial for cells to generate a certain amount of dopamine. In this first step of dopamine production, tyrosine-hydroxylase is used; whereas aromatic L-amino acid decarboxylase is responsible for the second part of the process. Interestingly, decarboxylation is a chemical reaction that involves the removal of the carboxyl group; therefore, the question "Does carbon dioxide released from the reaction damage the neurons?" comes to mind. It is stated again in the same article that "dopamine synthesis does not result in dopamine accumulation," showing that dopamine production is not a negative feedback loop (Segura-Aguilar et al., 2014).

On the other hand, dopamine serves diverse functions as a neurotransmitter, acting as a chemical messenger in the brain and central nervous system, playing important roles in regulating both various physiological and psychological functions. From Molecular Neurobiology Laboratory at Korea University, Dr. Ja-Hyun Baik discusses that "[dopaminergic] neurons originate in [the substantia nigra] and project to the striatum, cortex, limbic system and hypothalamus. Through these pathways, [dopamine] affects many physiological functions, such as the control of coordinated movements and hormone secretion, as well as motivated and emotional behaviors" (Baik, 2013). It is understood that those dopaminergic pathways exhibit structural and functional variations, yet their key functions encompass mood regulation, motor control, and reward and pleasure-related behaviors. It is worth noting that dopamine's functions are interconnected and extend beyond just the brain, as it is also present in various organs and systems. However, this paper will focus on the motor and non-motor functions of dopamine.

Zooming out from the dopamine production at the cellular level and its functions in the body, the substantia nigra, where the dopamine-producing neurons are mostly located may signify the evolutionary advantage of having those dopaminergic neurons in such a middle part of the brain, since substantia nigra interferes with other parts of the brain often. An article published by Neuroimaging Clinics of North America indicates that substantia nigra "(...) is divided into 2 anatomically and functionally distinct parts: the inferior (caudal) and posterior (dorsal) SN pars compacta (SNc) containing melanized neurons, and the superior (rostral) and anterior (ventral) SNr," (Massey and Yousry, 2010). Especially, the SNc nucleus appears to be crucial in containing most of the dopaminergic neurons and projecting them to other parts of the brain. Referring to the first article from Shankar Chinta and Julie Andersen, again, SNc is the origin of some important mesencephalic dopaminergic systems as it states that "the nigrostriatal system, the best-known dopaminergic system,

originates in the zona compacta of the substantia nigra (SNc) and extends its fibers into the dorsal striatum," (Chinta and Andersen, 2005). Supporting the crucial role of SNc in dopaminergic systems, Prof. Groenewegen mentions that "the pars reticulata most resembles the internal segment of the pallidum, while the pars compacta contain the dopaminergic neurons that project to both the striatum and the (pre)frontal cortex," in his article on basal ganglia and motor control, emphasizing the essential role of dopamine-producing neurons in SNc within motor control systems and circuits (Groenewegen, 2003).

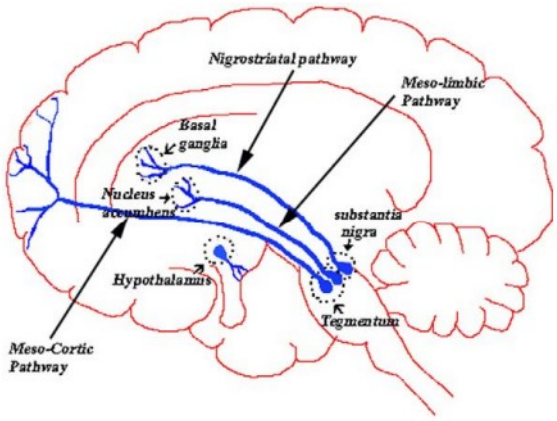

Figure 1: The representation of dopaminergic pathway system in human brain, adopted from Chinta and Andersen, 2005.

Furthermore, it is important not to confine the origins of dopaminergic pathways solely to the substantia nigra. As can be seen in Figure 1, certain dopaminergic pathways originate in another midbrain structure known as the tegmentum. The dopaminergic neurons in this neural area are commonly referred to as dopaminergic neurons in the ventral tegmental area. However, Figure 1 also illustrates the presence of several unlinked dopaminergic cell groups distributed across various parts of the brain, for instance, in the hypothalamus. Therefore, dopaminergic pathways are located in different locations of the brain, each projecting dopaminergic neurons to different parts of the brain, and each responsible for a range of both different and similar functions. These dopaminergic pathways and their functions will be further explored in section 2.

On the other hand, the answer to the question "How dopamine travels in dopaminergic pathways?" requires investigation at the level of a ligand–receptor protein relationship. Since dopamine is a neurotransmitter, this will eventually be an indicator of the presence of a G protein-coupled type protein receptor family, dopamine receptors. An article published in Clinica Chimica Acta, the International Journal of Clinical Chemistry, states that "There are five subtypes of dopamine receptors including D1, D2, D3, D4, and D5 [...]. These subtypes are further divided into two subclasses, D1-like family receptors (types 1 and 5)

and D2-like family receptors (types 2, 3, and 4)" (Latif et al., 2021). It is also stated in the same article that the sub-classing of dopamine receptors is based on structural similarities, and even with respect to the drug sensitivity in the case of D1 and D5 (Latif et al., 2021). D1 receptors are involved in dopaminergic-controlled cognitive processes like memory and attention, whereas, D2 receptors have the ability to regulate mood, control movement in the basal ganglia, and stabilize emotions in the limbic system. The different distribution patterns in the central nervous system, activation mechanisms, antagonist and agonist-binding affinities, and other factors contribute to the differences between D1 and D2 receptors. Moreover, Dr. Ja-Hyun Baik discusses that "the D1-like receptors [...] stimulate intracellular cAMP levels, comprising D1 and D5, and the D2- like receptors [...] inhibit intracellular cAMP levels, comprising D2, D3, and D4 receptors" (Baik, 2013). Connecting the direct proportionality between the cAMP and the motor functions (movement) to the information taken from Dr. Baik's article, the activation of D1-like receptors facilitates intended motor movements within the direct pathway (D1- positive), whereas, the activation of D2-like receptors suppresses unwanted motor movements in the indirect pathway (D2-positive).

3 Etiology and pathology of Parkinson's Disease

The term "etiology" refers to the study of the origins, causes, or factors that contribute to the progression of a specific disease or phenomenon. It serves to comprehend the underlying causes or triggers of a condition within the realm of healthcare. Parkinson's disease is a progressive neurodegenerative disorder, meaning that the disease is triggered by the loss of structure or function of neurons and worsens with time. The etiology of Parkinson's disease is complex and involves genetic, environmental, and neurological factors. Although ongoing research has provided significant insight into potential disease origins, its exact etiology remains incompletely understood. Yet, the origins of Parkinson's disease can be further examined within inter-connected categories as such: genetic factors, environmental risks, age, mitochondrial dysfunction, neuroinflammation, alpha-synuclein accumulation, and oxidative stress.

Epigenetics refers to changes in gene expression that are often reversible, inheritable, and not permanently encoded in the DNA sequence. Data taken from a Cell Press journal article indicates that "familial forms of PD account for only about 10–15

Moreover, insights from Maria Angeliki Pavlou, a postdoctoral researcher at the University of Luxembourg, and Prof. Dr. Tiago Fleming Outeiro from the University of Göttingen reveal that "the list of genes implicated in the onset of PD (PARK genes) is continually expanding," and "the PARK gene family currently comprises 20 genes" (Pavlou and Outeiro, 2017). Remarkably, a close relationship exists between the accumulation of alpha-synuclein, a protein found in neurons that controls the movement of synaptic vesicles and the resulting release of neurotransmitters, and the epigenetics of the disease: Alpha-synuclein

Locus	Gene	Gene product	Inheritance/ PD onset	Chromosomal locus
PARK1/PARK4	*SNCA*	Alpha-synuclein (aSyn)	AD/EO	4q21.3-q22
PARK2	*PARKIN*	Parkin RBR E3 ubiquitin protein ligase	AR/EO	6q25.2-q27
PARK3	Unknown	Unknown	AD	2p13
PARK5	*UCHL1*	Ubiquitin C-terminal hydrolase L1	AD	4p13
PARK6	*PINK1*	PTEN induced putative kinase 1	AR/EO	1p36.12
PARK7	*DJ-1*	DJ-1	AR/EO	1p36.23
PARK8	*LRRK2*	Leucine-rich repeat kinase 2 (LRRK2)	AD/EO and LO cases	12q12
PARK9	*ATP13A2*	ATPase type 13A2 (ATP13A2)	AR/EO	1p36
PARK10	Unknown	AAOPD	Susceptibility	1p32
PARK11	Unknown	GIGYF2 (GRB10 interacting GYF protein 2)	AR/EO	2q36-q37
PARK12	Unknown	Unknown	Susceptibility	Xq21-q25
PARK13	*HTRA2*	HtrA serine peptidase 2	AD	2p13.1
PARK14	*PLA2G6*	Phospholipase A2 group VI	AR/LO	22q13.1
PARK15	*FBXO7*	F-box protein 7 (FBXO7)	AR/EO	22q12.3
PARK16	Unknown	Unknown	Susceptibility	1q32
PARK17	*VPS35*	VPS35 retromer complex component	AD/LO	16q12
PARK18	*EIF4G1*	Eukaryotic translation initiation factor 4 gamma 1	AD/LO	3q27.1
PARK19	*DNAJC6*	Auxilin	AR/EO	1p31.3
PARK20	*SYNJ1*	Synaptojanin-1	AR/EO	21q22.11

AD autosomal dominant, *AR* autosomal recessive, *EO* early onset, *LO* late onset

Figure 2: : Genes related to familial forms of PD (PARK genes), adopted from Pavlou and Outeiro, 2017.

(SNCA) gene mutations were the first to be linked to familial Parkinson's disease. (Pavlou and Outeiro, 2017).

Figure 2 affirms the presence of both autosomal dominant and autosomal recessive genes that are related to the disease. However, the SNCA gene stands out as the first associated with familial PD and an autosomal dominant gene. Bobby Thomas, a professor from the Medical University of South Carolina, and M. Flint Beal, a former chair of the Department of Neurology at Weill Cornell Medicine, claim that "[the] three missense mutations in a-synuclein gene (A53T, A30P and E46K), and in addition to genomic triplications of a region of a-synuclein gene are associated with autosomal dominant PD" (Thomas and Beal, 2007). However, some claims that "[p]recently, six-point mutations [...] have been linked with autosomal dominant forms of PD with duplications and triplications of the SNCA locus have also been associated with autosomal dominant forms of PD" (Pavlou and Outeiro, 2017). The difference between data indicates a progressive understanding of the genetic background of the disease, taking into consideration the publication timeline of the sources.

Alpha-synuclein is a protein coded by SNCA gene and responsible for vesicle trafficking, vesicle docking and priming, vesicle fusion, and neurotransmitter release, and axonal transport- all of which are key components of neural communication in neural pathways. Consequently, when the SNCA gene mutates, it is expected to produce misfolded alpha-synuclein proteins that interfere with neuronal functions. "Importantly, alpha-synuclein is a major component of Lewy bodies and Lewy neurites, the pathological hallmarks of PD," states Prof. Jankovic (Jankovic and Tan, 2020). Lewy bodies consist of misfolded alpha-synuclein proteins and accumulate inside neurons, playing a significant role in disease progression and the development of both motor and non-motor symptoms.

Moreover, Prof. Jankovic further suggests that "abnormal aggregation of the protein [alpha-synuclein] has been found to be toxic to dopaminergic neurons leading to neurodegeneration associated with PD" (Jankovic and Tan, 2020). Especially, those Lewy bodies containing abnormally folded alpha-synuclein accumulate in the substantia nigra, disrupting the function of dopaminergic neurons in SNc. As dopaminergic neurons degenerate, dopamine levels decrease drastically, resulting in dopamine depletion. Therefore, the motor symptoms of PD, such as bradykinesia (slowness of movement), rigidity, and resting tremors can be justified as a result of Lewy pathology. On the other hand, beyond the substantia nigra, Lewy bodies are also located in brain regions related to mood regulation, cognition, and autonomic function. The non-motor symptoms of Parkinson's disease, such as cognitive impairment, mood disorders, sleep issues, and autonomic dysfunction, are influenced by the widespread presence of Lewy bodies. The accumulation of Lewy bodies in areas related to cognition may even lead to another condition known as Lewy body dementia (LBD), which is another area of research.

Still, two researchers from Toronto University argue that "[the] important findings over the past several years have revealed that Parkinson's disease pathology is more complex than neurodegeneration due to Lewy pathology alone" (Kalia and Lang, 2015). At this very point, mitochondrial dysfunction represents another well-known factor in the pathogenesis of the disease.

Parkinson's disease development is thought to be significantly influenced by mitochondrial dysfunction. Mitochondria are crucial organelles for cellular energy production in the form of adenosine triphosphate (ATP). Therefore, increased oxidative stress and impaired energy generation are only two cellular concerns that might result from mitochondrial malfunctioning. On the one hand, dopamine-producing neurons, particularly those in SN, are highly energy-demanding and heavily reliant on proper mitochondrial function. Impaired energy generation caused by mitochondrial malfunctioning, therefore, restricts the neurons from generating energy, leading to reduced dopamine production. On the other hand, severe oxidative stress can cause cell death as a result of disrupted mitochondrial respiration. Thus, the loss of dopamine-producing neurons and the ensuing non-motor and motor symptoms can be justified by both outcomes of mitochondrial dysfunction.

At this point, consideration of the molecular mechanisms underlying Lewy

bodies raises the question of whether there is an inter-relatedness between epigenetics of the disease and mitochondrial dysfunction pathology. A group of researchers from the University of Lübeck and the University of Luxembourg, including medical professional Max Borsche, claim that "the most compelling evidence for a direct link between mitochondria and PD has been established for the autosomal recessively inherited PD genes Parkin, PINK1, and DJ-1" (Borsche et al., 2021). Referring back to Table 1, it is seen that these genes correspond to PARK2, PARK6, and PARK7 respectively.

Furthermore, it is stated in another article that the amygdala, frontal brain, cerebellum, and substantia nigra of PD patients exhibit considerably lower levels of miR-34b and c, two types of micro RNA, along with a decrease in the expression of PARK2 and PARK7 (Pavlou and Outeiro, 2017). The thesis of a possible inter-relatedness between PARK 2 - PARK 7 genes and mitochondrial dysfunction is well-supported as Pavlou and Outeiro further reveal that "[the] depletion of miR34-b and c in in vitro differentiated dopaminergic neurons caused an alteration of mitochondrial function and oxidative stress" (Pavlou and Outeiro, 2017). Hereby, Parkin and DJ-1 genes are proven to have an influence on both mitochondrial dysfunction and a possible following neurodegeneration.

Still, the two pathologies discussed above, Lewy pathology and mitochondrial dysfunction pathology, are not necessarily triggered independently. Remarkably, the production of reactive oxygen species (ROS) as a result of oxidative stress can interfere with cellular proteins, including alpha-synuclein. Therefore, it is understood that mitochondrial dysfunction resulting in oxidative stress may trigger alpha-synuclein's misfolding and accumulation into Lewy bodies. Conversely, the reverse scenario is also supported, as misfolded alpha-synuclein can attach to mitochondrial membranes, disrupting their structure and function and further exacerbating mitochondrial dysfunction. At the end of both pathologies, the neurodegeneration of dopamine-producing neurons, regardless of where they are located, is inevitable.

Depending on which dopaminergic neurons degenerate and where in the brain this degeneration takes place, the symptoms of Parkinson's disease may vary. Since different parts of the brain are responsible for various functions, it could lead to a particular set of symptoms when dopaminergic neurons degenerate in particular places. In reference to an article published by Anthony Schapira, a neurological science professor at University College London, and Roberta Balestrino, a PhD student; the motor symptoms of PD have a wide range, including tremor, bradykinesia (slowness of movement), rigidity, postural instability, disturbances of speech, and alteration in blinking and eye movements (Balestrino and Schapira, 2020). Moreover, objecting to the classic emphasis on motor symptoms in understanding PD, it is revealed in the same article that even though PD has been historically associated with movement disorders, clinical analysis shows that non-motor symptoms – including autonomic, gastrointestinal, sleep, sensorial, cognitive and neuropsychiatric disturbances – also have a significant impact on patient's quality of life (Balestrino and Schapira, 2020).

As discussed in Section 1, the SNc contains the majority of dopaminergic

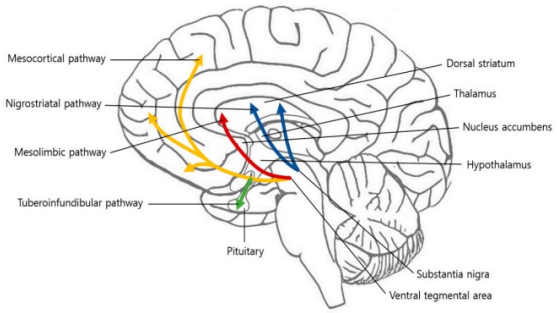

Figure 3: The 4 main dopaminergic pathways of brain, adopted from Seoyon Yang et al., 2020.

neurons in the brain and projects them to the striatum, a pivotal part of the basal ganglia circuitry. This pathway is known as the nigrostriatal pathway and plays a crucial role in regulating voluntary movement. Kaitly Cramb, a post-graduate researcher at Oxford University in the physiology, anatomy, and genetic department, along with a group of researchers, further claimed that "[a]s hallmarks of Parkinson's disease, the death of dopaminergic neurons and reduction of striatal DA are frequently referred to interchangeably in reports of Parkinson's disease studies" (Cramb et al., 2023). Therefore, it is understood that the degeneration of dopaminergic neurons in the nigrostriatal pathway often results in motor symptoms such as bradykinesia and tremors.

Supporting the information given, in an article published by Neurologist Prof. Michael Krasnianski and a group of researchers, it is stated that "the dopamine-dependent movement regulation at the nigrostriatal level occurs by modulation of tone and contraction in skeletal muscles through the action of nano- or micromolar dopamine concentrations on the postsynaptic D1 and D2 receptors" (Korchounov et al., 2010). Thus, dopamine plays an important role as a neurotransmitter in regulating voluntary movement through both D1 and D2 type receptors in the nigrostriatal pathway, and the dopaminergic neurodegeneration leads to loss of motor functions.

Other dopaminergic pathways, such as nigropallidal and nigrothalamic pathways, also form part of the basal ganglia circuitry and are involved with voluntary movement. Likely, the loss of dopaminergic neurons in these pathways results in motor symptoms associated with Parkinson's disease. Moreover, a paper published via Europe PMC Funders Group extends the range of motor symptoms of PD as it states that the basal ganglia are found to be crucial for habitual control, and the most common symptoms of the disease may reflect a relative decrease in the expression of habitual behaviors due to dopamine loss in regions linked to habitual control (Redgrave vd., 2010). This may damage the reward-learning mechanism of the brain.

Disruptions in the balanced output from the striatum to the SNc can lead to other motor symptoms such as dyskinesia when the degeneration of dopaminer-

gic neurons occurs in the striatonigral pathway. The results of a research paper published by the British Pharmacological Society show that in a mouse model of Parkinson's disease, selective activation of the striatonigral terminals resulted in dyskinesia (Keifman et al., 2019). It can be derived that the loss of dopaminergic neurons results in over-expression of striatonigral terminals, indicating a regulatory function of dopaminergic neurons in this pathway. According to an experiment performed by a group of professors from Columbia University, selective optogenetic stimulation of striatonigral pathway synapses in vivo revealed that "DA denervation sensitized striatonigral-mediated stimulation of motor activity in hemiparkinsonian mice" (Borgkvist et al., 2015). Thus, the altered striatonigral pathway is also responsible for the progression of motor symptoms in the disease. On the other hand, Parkinson's disease's non-motor symptoms can result from neurodegeneration in non-dopaminergic pathways. However, they can be triggered by some disrupted dopaminergic pathways as well. Dag Aarsland, a professor of Old Age Psychiatry at King's College London, and his team state in their paper that "mesolimbic and mesocortical dopaminergic activity is associated with cognitive functioning" (Aarsland et al., 2017). This raises the question of how can dopaminergic pathways differentiate in terms of non-motor and motor functionality.

Nathan Bridges, a clinical support specialist at Sanesco, indicates in his paper that both mesolimbic and mesocortical pathways originate from the ventral tegmental area, which is in close proximity to the SN. The mesolimbic pathway projects dopaminergic neurons to the nucleus accumbens, whereas the mesocortical pathway projects to the prefrontal cortex (Bridges, 2016). Furthermore, in the mesolimbic pathway, dopamine mediates feelings of pleasure and reward whereas; the mesocortical pathway is involved in cognition, working memory, and decision-making. In this context, the specific projection of dopaminergic neurons determines the functions of these pathways. However, the source of origin is also a key determinant, with those originating from the SN generally involved in motor functions, and those originating from VTA in non-motor functions of the brain. Taking both propositions into account, there exists a clear relationship between the structures of pathways, their functions, and the symptoms that result in Parkinson's disease.

Interestingly, both pathways responsible for motor and non-motor symptoms of the disease can be interconnected, as evidenced by the cortico-basal ganglia-thalamo-cortical loop. An article published on Elsevier suggests the "dimmer-switch model" for this case, which states that the dopaminergic neurons' degeneration in the basal ganglia is responsible for tremors, while the cerebello-thalamo-cortical is responsible for the amplification of tremors due to disruptions in cognitive function of the brain (Helmich et al., 2012). Lastly, the tuberoinfundibular pathway can be cited as another example where dopamine serves as a regulator/inhibitor. By inhibiting the release of prolactin from the pituitary gland, this pathway contributes to the hormonal balance (Bridges, 2016). Therefore, non-motor symptoms of the disease, like hormonal imbalances that are affecting sexual function and menstruation, may result from dysfunction in this pathway. Still, the interconnectedness of all those pathways reveals the

complex and heterogeneous nature of Parkinson's disease.

4 Conclusion

In this review, the link between dopamine and Parkinson's disease is explored by investigating the causes of dopaminergic neuron degeneration and the resulting symptoms arising from different pathways in which neurodegeneration is observed. We commence by delving into the fundamental aspects of dopamine and its role within the body. This includes an examination of the chemical background of dopamine, followed by the identification of the primary brain regions housing dopaminergic neurons. Furthermore, dopamine receptors are discussed and classified as D1-like or D2-like, to gain a comprehensive understanding of how dopamine acts as a chemical messenger in dopaminergic pathways. Subsequently, our focus shifts to the etiology and pathology of Parkinson's disease, aiming to unravel the interconnected pathologies behind Parkinson's disease. We explore the association between Lewy body and mitochondrial dysfunction pathologies and the genetic background of Parkinson's disease. Hereby, the loss of dopaminergic neurons in Parkinson's disease due to those pathologies is seen. Some important dopaminergic pathways are discussed and classified according to the general motor and non-motor symptoms they result in. Overall, the link between dopamine and Parkinson's disease is clarified: The depletion of dopamine in dopaminergic pathways, due to neurodegeneration caused mostly by Lewy body and mitochondrial dysfunction pathologies in Parkinson's disease, results in a range of motor and non-motor disabilities in patients. The complexity of the disease presents a significant challenge for the development of definitive treatments. However, L-DOPA can be used as a treatment method in which the L-DOPA uptake of dopaminergic neurons is stimulated since L-DOPA is converted into dopamine afterward. Moreover, for addressing Lewy body pathology in the disease, specific genes that are mutated and responsible for the production of misfolded alpha-synuclein can be inhibited by the techniques of "knock-down" or "knock out" using CRISPR technology. The same method can be also applied to mitochondrial dysfunction, given the involvement of specific genes in the progression of the disease in this pathway as well. Therefore, the most promising approach to the treatment of the disease appears to lie in gene manipulation. It is accepted that the current knowledge of the genetic mechanisms behind Parkinson's disease is not sufficient. Therefore, it is imperative to encourage and fund more research on this topic in order to find a permanent solution for the disease. Until then, physical and occupational therapy, regular exercise, and psychological and emotional support seem to decrease the severity of symptoms of the disease for patients. Still, it is crucial to recognize that Parkinson's disease is a progressive condition, and as symptoms change over time, treatment strategies may require periodic adjustments.

References

[ACP+17] Dag Aarsland, Byron Creese, Marios Politis, K. Ray Chaudhuri, Dominic H. ffytche, Daniel Weintraub, and Clive Ballard. Cognitive decline in parkinson disease. *Nature Reviews Neurology*, 2017.

[Bai13] Ja-Hyun Baik. Dopamine signaling in reward-related behaviors. *Frontiers in Neural Circuits*, 2013.

[BAW+15] Anders Borgkvist, Elizabeth M. Avegno, Minerva Y. Wong, Mazen A. Kheirbek, Mark S. Sonders, Rene Hen, and David Sulzer. Loss of striatonigral gabaergic presynaptic inhibition enables motor sensitization in parkinsonian mice. *Neuron*, 2015.

[BPKG21] Max Borsche, Sandro L. Pereira, Christinea Klein, and Annea Grünewald. Mitochondria and parkinson's disease: Clinical, molecular, and translational aspects. *Journal of Parkinson's Disease*, 2021.

[Bri16] Nathan Bridges. Dopamine pathways. *Sanesco Health*, 2016.

[BS20] Roberta Balestrino and Anthony Henry Vernon Schapira. Parkinson disease. *European Journal of Neurology*, 2020.

[CA05] Shankar J. Chinta and Julie K. Andersen. Dopaminergic neurons. *The International Journal of Biochemistry Cell Biology*, 2005.

[CBKCWM23] Kaitlyn M. L. Cramb, Dayne Beccano-Kelly, Stephanie J. Cragg, and Richard Wade-Martins. Impaired dopamine release in parkinson's disease. *Brain : A Journal of Neurology*, 2023.

[Gro03] Henk J. Groenewegen. The basal ganglia and motor control. *Neural Plasticity-Forward Series*, 2003.

[HHD+12] Rick C. Helmich, Mark Hallett, Günther Deuschl, Ivan Toni, and Bastiaan R. Bloem. Cerebral causes and consequences of parkinsonian resting tremor: a tale of two circuits? *Brain : A Journal of Neurology*, 2012.

[HJF+16] Lauren Hirsch, Nathalie Jette, Alexandra Frolkis, Thomas Steeves, and Tamara Pringsheim. The incidence of parkinson's disease: A systematic review and meta-analysis. *Neuroepidemiology*, 2016.

[JT20] Joseph Jankovic and Eng King Tan. Parkinson's disease: Etiopathogenesis and treatment. *Journal of Neurology, Neurosurgery, and Psychiatry*, 2020.

[KL15] Lorraine V Kalia and Anthony E Lang. Parkinson's disease. *Lancet*, 2015.

[KMK10] Alexei Korchounov, Michael F. Meyer, and Michael Krasnianski. Postsynaptic nigrostriatal dopamine receptors and their role in movement regulation. *Journal of Neural Transmission*, 2010.

[KRDP+19] Ettel Keifman, Irene Ruiz-DeDiego, Diego Esteban Pafundo, Rodrigo Manuel Paz, Oscar Solís, Mario Gustavo Murer, and Rosario Moratalla. Optostimulation of striatonigral terminals in substantia nigra induces dyskinesia that increases after l-dopa in a mouse model of parkinson's disease. *British Journal of Pharmacology*, 2019.

[LJR+21] Saad Latif, Muhammad Jahangeer, Dure Maknoon Razia, Mehvish Ashiq, Abdul Ghaffar, Muhammad Akram, Aicha El Allam, Abdelhakim Bouyahya, Larisa Garipova, Mohammad Ali Shariati, Muthu Thiruvengadam, and Mohammad Azam Ansari. Dopamine in parkinson's disease. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, 2021.

[MY10] Luke Massey and Tarek Yousry. Anatomy of the substantia nigra and subthalamic nucleus on mr imaging. *Neuroimaging Clinics of North America*, 2010.

[Par17] James Parkinson. An essay on the shaking palsy. *Project Gutenberg*, 1817.

[PO17] Maria Angeliki S. Pavlou and Tiago Fleming Outeiro. Epigenetics in parkinson's disease. *Advances in Experimental Medicine and Biology*, 2017.

[RRS+10] Peter Redgrave, Manuel Rodriguez, Yoland Smith, Maria C. Rodriguez-Oroz, Stephane Lehericy, Hagai Bergman, Yves Agid, Mahlon R. DeLong, and Jose A. Obeso. Goal-directed and habitual control in the basal ganglia: Implications for parkinson's disease. *Nature Reviews Neuroscience*, 2010.

[TB07] Bobby Thomas and M. Flint Beal. Parkinson's disease. *Human Molecular Genetics*, 2007.

[YBRCC20] Seoyon Yang, Mathieu Boudier-Revéret, Yoo Jin Choo, and Min Cheol Chang. Association between chronic pain and alterations in the mesolimbic dopaminergic system. *Brain Sciences*, 2020.