



**HAL**  
open science

## Parkinson disease: Protective role and function of neuropeptides

Mireille Tabikh, Charbel Chahla, Nathalie Okdeh, Hervé O Kovacic,  
Jean-Marc Sabatier, Ziad Fajloun

► **To cite this version:**

Mireille Tabikh, Charbel Chahla, Nathalie Okdeh, Hervé O Kovacic, Jean-Marc Sabatier, et al..  
Parkinson disease: Protective role and function of neuropeptides. *Peptides*, 2022, 151, pp.170713.  
10.1016/j.peptides.2021.170713 . hal-03566584

**HAL Id: hal-03566584**

**<https://amu.hal.science/hal-03566584>**

Submitted on 22 Jul 2024

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

**Title:**

**Parkinson disease: protective role and function of neuropeptides**

Short title: Neuropeptides' effect on PD

**Authors:**

Mireille Tabikh<sup>a,†</sup>, Charbel Chahla<sup>a,†</sup>, Nathalie Okdeh<sup>a</sup>, Herve Kovacic<sup>b</sup>, Jean-Marc Sabatier<sup>b,\*</sup>, Ziad Fajloun<sup>a,c,\*</sup>

**Affiliations:**

<sup>a</sup> Faculty of Sciences 3, Department of Biology, Lebanese University, Campus Michel Slayman Ras Maska, 1352 Tripoli, Lebanon

<sup>b</sup> Faculté de Médecine, Université Aix- Marseille, Institut de Neuro-Physiopathologie, UMR 7051, Boulevard Pierre Dramard- CS80011, 13344 Marseille Cedex 15, France

<sup>c</sup> Laboratory of Applied Biotechnology (LBA3B), Azm Center for Research in Biotechnology and its Applications, EDST, Lebanese University, 1300 Tripoli, Lebanon

† Equal contribution

\* Corresponding authors: Drs Jean Marc Sabatier and/or Ziad Fajloun, E-mails :  
sabatier.jm1@gmail.com (JMS) and zfajloun@gmail.com (ZF)

24 **Abstract**

25 Neuropeptides are bioactive molecules, made up of small chains of amino acids, with many  
26 neuromodulatory properties. Several lines of evidence suggest that neuropeptides, mainly expressed  
27 in the central nervous system (CNS), play an important role in the onset of Parkinson’s Disease  
28 (PD) pathology. The wide spread disruption of neuropeptides has been excessively demonstrated to  
29 be related to the pathophysiological symptoms in PD where impairment in motor function per  
30 example was correlated with neuropeptides dysregulation in the substantia niagra (SN). Moreover,  
31 the levels of different neuropeptides have been found modified in the cerebrospinal fluid and blood  
32 of PD patients, indicating their potential role in the manifestation of PD symptoms and  
33 dysfunctions. In this review, we outlined the neuroprotective effects of neuropeptides on  
34 dopaminergic neuronal loss, oxidative stress and neuroinflammation in several models and tissues  
35 of PD. Our main focus was to elaborate the role of orexin, pituitary adenylate cyclase activating  
36 polypeptide (PACAP), vasoactive intestinal peptide (VIP), opioids, angiotensin, carnosine and  
37 many others in the protection and/or involvement in the neurodegeneration of striatal dopaminergic  
38 cells. Further studies are required to better assess the mode of action and cellular mechanisms of  
39 neuropeptides in order to shift the focus from the *in vitro* and *in vivo* testing to applicable clinical  
40 testing. This review, allows a support for future use of neuropeptides as therapeutic solution for PA  
41 pathophysiology.

42

43 **Keywords:**

44 Parkinson disease, neuropeptide, orexin, PACAP, VIP, opioid, angiotensin, carnosine

45

46

47

48

49

50

51

## 52 1. Introduction

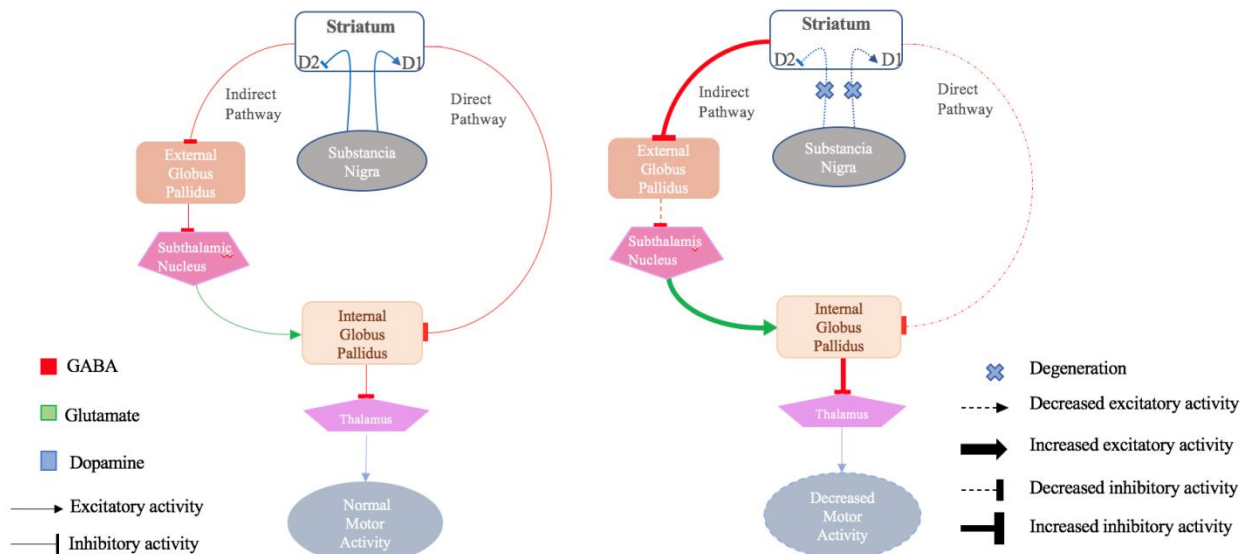
53 Parkinson's disease (PD) is one of the most common neurodegenerative diseases, second only to  
54 Alzheimer's disease with a late onset of 40-60's years of age [1]. Traditionally, it's characterized by  
55 dopaminergic degeneration in the substantia nigra pars compacta (SNpc), a midbrain basal ganglia  
56 structure implicated mainly in movement, with a deposition of insoluble cytoplasmic proteins in  
57 surviving cells called "Lewy bodies". PD leads to an abundance of motor dysfunctions such as  
58 bradykinesia (slowness of movements), muscular rigidity, rest tremor, and postural and gait  
59 impairment [2,3]. Several other brain structures are also involved in PD pathophysiology: lesions in  
60 all of 13 nuclei in the hypothalamus were linked to sleep disorders and cognitive impairment. The  
61 posterior cingulum, a limbic lobe structure activated during retrieval of episodic memory, is  
62 affected by the neurodegeneration, astrogliosis and demyelination in PD [4]. Besides the  
63 involvement of many brain regions, even peripheral tissues are affected by PD such as the  
64 cardiovascular system, the urinary tract, the skin and sweat glands, gastrointestinal tract, and the  
65 neuroendocrine structures. As a result, PD comes with other non-motor symptoms summarized by  
66 affective, cognitive, dizziness, olfactory dysfunctions among many others [5]. This broad range of  
67 disabling symptoms causes not only a reduction of quality of life but also an emotional and  
68 economic burden on the caregivers [6].

## 69 2. Parkinson's disease pathophysiology

### 70 *2.1. Direct/indirect pathways*

71 In the direct pathway, the substantia nigra activates D1 receptors, via dopaminergic stimulation,  
72 leading to the activation of GABAergic MSNs (striatal medium spiny neurons, targets of gamma-  
73 aminobutyric acid) that inhibits the internal pallidum, leading to the disinhibition of the thalamic  
74 glutamatergic neurons that have an excitatory glutamatergic action on the cortex. This leads to  
75 locomotor activation. Conversely, in the indirect pathway, the substantia nigra (SN) activates D2  
76 receptors which inhibits the GABAergic neurons on the external pallidum, leading to the  
77 disinhibition of the glutamatergic neurons of the sub thalamic nucleus (STN). These in turn  
78 activates the internal pallidum's GABAergic neurons that project to the thalamus. This results in the

79 reduction of locomotor activity. PD is a result of dopamine (DA) depletion in the SN pars compacta  
 80 which results in an overstimulation in the indirect pathway and a reduced activation of the direct  
 81 pathway. Thus, causing overall reduced locomotor activity [7] (Figure 1).



82

83 Figure 1. SN modality role is executed through dopaminergic projection to the striatum with D1 excitatory  
 84 synapse and D2 inhibitory synapse. The downstream effect of nigrostriatal D1 excitation of the striatum will  
 85 result in an inhibition of the internal Globus Pallidus by GABAergic projection from the striatum to the  
 86 internal globus pallidus through the direct pathway. Its inhibition will allow the activation of motor activity  
 87 through the thalamus. In the indirect pathway, the SN will inhibit the GABAergic inhibitory projection from  
 88 the striatum to the external globus pallidus, this will therefore allow the subthalamic nucleus to activate the  
 89 internal globus pallidus through glutamate projection in order to inhibit the thalamus and result in the  
 90 inhibition of the motor activity. Therefore, the SN will allow motor activity through the direct pathway and  
 91 inhibit it through the indirect pathway. In the PD case, SN modulation of the striatum is attenuated by the  
 92 dopaminergic degeneration. The activity of the direct pathway will be decreased, and the activity of the  
 93 indirect pathway will be increased, leading to the overinhibition of the thalamus that will decrease the motor  
 94 activity.

## 95 2.2. Alpha synuclein

96  $\alpha$ -synuclein is a 140 amino acid protein mostly found in the brain, especially in dopaminergic  
 97 neurons of the SN in form of Lewy bodies [8].  $\alpha$ -synuclein's proper structure hasn't been clearly  
 98 identified, which is why its termed as a natively unfolded protein. It can have several

99 conformations: monomeric, fibrillar,  $\alpha$ -helical,  $\beta$ -pleated sheet and an amyloid structure in the  
100 fibrils of Lewy bodies, a hallmark of PD pathophysiology [9,10]. Mutations occurring in the 3  
101 domains of  $\alpha$ -synuclein lead to its pathological folding, oligomerization, formation of fibrils that  
102 leads to Lewy bodies, are responsible of the toxicity induced by  $\alpha$ -synuclein found in familiar PD  
103 [11].  $\alpha$ -synuclein is expressed in all brain regions, however, Lewy bodies and neurodegenerations  
104 are abundant especially in the SNpc. This could be related to the major presence of the DA neurons  
105 in the SN. In fact, during the metabolism of DA, reactive oxygen species (ROS) that stimulate  
106 apoptosis, might interact with the  $\alpha$ -synuclein and aggregation them into protofibrils. The latter  
107 have been shown to play major role in  $\alpha$ -synuclein toxicity [10].

### 108 ***2.3. Oxidative stress neural inflammation and mitochondrial dysfunction***

109 The pathophysiological hallmark of PD is indisputably considered as the neurodegeneration of  
110 SNpc dopaminergic projection to the striatum. But the true origin of such insult is a subject of  
111 discussion. Hence, many theories are trying to decipher the underlying cause of DA neurons death.  
112 The literature presents oxidative stress, neural inflammation, and mitochondrial dysfunction to  
113 converge and intertwine to cause cellular death and degeneration [12]. In fact, oxidative stress is  
114 manifested when the balance is disrupted between the ROS being produced and accumulated in  
115 cells and tissues, and their detoxification by the biological system [13]. Superoxide, hydroxyl  
116 radical, peroxynitrite, and  $H_2O_2$  are ROS that are produced by the biological system through  
117 enzymatic or non-enzymatic reactions. At low concentration, they can present a physiological  
118 cellular role such as in macrophage phagocytosis. But at higher concentration, they can alter and  
119 damage several structures in the cell such as membrane, organelles, and even DNA leading to many  
120 chronic and neurodegenerative diseases [14]. Innately dopamine neurons are highly susceptible to  
121 exhibit high ROS levels and oxidative stress: (i) they require a large amount of energy and have  
122 long axons of 1-4-meter-long and a large number of synapses which are hard to sustain and require  
123 high energy consumption; (ii) they exhibit an increased level of cytosolic dopamine and its  
124 metabolite which can cause toxicity ROS formation [12].

125 Neural inflammation is another player of PD neurodegeneration evidenced by the increase in pro-  
126 inflammatory cytokines and factors in PD patients and animal models [15, 16]. One of the major  
127 players of neural inflammation are microglial cells. These cells are residing macrophages in the  
128 brain tissue responsible for monitoring brain homeostasis. Microglial cells can be activated into M1

129 phenotypes (proinflammatory) or M2 (anti-inflammatory) phenotype. Misfolded proteins and toxins  
130 lead to the hyperactivation of the M1 phenotypes microglia in PD animal models. This  
131 hyperactivation is theorized to cause DA cell death by phagocytosis of the neurons and by the  
132 increase of ROS formation through inducible nitric oxide synthase (iNOS) and nitric oxide  
133 synthase (NOS) Enzymes [17].

134 Dysregulated mitochondrial protein, DNA, and function in PD hint at the involvement of  
135 mitochondrial dysfunction in PD pathology of sporadic and familial PD [18,19]. Changes in  
136 mitochondrial morphology and dynamic, inhibition of complex I of electron-transport chain, and  
137 formation of ROS lead to cell energetic failure and toxicity and eventually degeneration [20].

### 138 3. Parkinson's disease models

139 Various toxins induce motor deficits occurring in PD. Among these toxins MPTP (1-Methyl-4-  
140 phenyl-1,2,3,6-tetrahydropyridine), 6-OHDA (6-hydroxydopamine), and rotenone. MPTP, after  
141 passing through the blood brain-barrier (BBB), is transformed by monoamine oxidase B into its  
142 active metabolite MPP<sup>+</sup>. The dopamine transporter (DAT) carries MPP<sup>+</sup> into dopaminergic  
143 neurons of the SNpc, where it stops mitochondrial complex I activity causing the death of these  
144 neurons. 6-OHDA, once injected locally (SNpc or medial forebrain bundle (MFB) due to its  
145 inability to cross the BBB), builds up in the cytosol of dopaminergic neurons and rapidly auto-  
146 oxidizes leading to the formation of high levels of hydrogen peroxide. Thus, causing the  
147 degeneration of the nigrostriatal pathway marking the highest level of nigral cell loss and striatal  
148 DA depletion obtainable in PD animal models. Rotenone, being highly lipophilic easily crosses the  
149 BBB, once in the cell, it stops complex I activity, leading to massive formation of ROS, and  
150 inhibition of the proteasome activity, thus causing proteolytic stress [21].

### 151 4. Neuropeptides

152 One of the main hypotheses proposed for PD pathology is the impairment in main protein's  
153 degradation systems, such as ubiquitin proteasome system (UPS) and autophagy-lysosomal  
154 pathways (ALP), that leads to accumulation of proteins, followed by cell toxicity and eventually  
155 cell death [22]. A proteomic analysis done in PD patients, showed that 221 proteins were  
156 dysregulated in the SN [23]. As well as in other biological samples, such as cerebrospinal fluid

157 (CSF), saliva and plasma, and other brain regions such as the caudate, the putamen and the globus  
158 pallidus where multiple dysregulations were found in several neuropeptides: Neuropeptide Y,  
159 Ghrelin, Substance P and Neurotensin [24]. Hence, the importance in studying the variation of the  
160 different neuropeptides in PD.

161 First and foremost, a peptide is a chain of 2 to 50 amino acids, joined by covalent binds, of 50 kD  
162 mass [25]. When it's secreted by the neurons in the brain it's called a "neuropeptide". By definition  
163 "a neuropeptide is a small proteinaceous substance produced and released by neurons through the  
164 regulated secretory route and acting on neural substrates". According to H. Burbach, there are three  
165 main pillars that identify neuropeptides: (i) their genes and proteins are, simultaneously, expressed  
166 and released by neurons; (ii) they are stored in dense vesicles and released when needed and (iii)  
167 they have the ability to regulate, via neuroreceptors, the functioning of neurons. Neuropeptides'  
168 release and activation is a multi-step progressive process from the endoplasmic reticulum, through  
169 the Golgi apparatus into secretory vesicles called dense core vesicles. All neuropeptides descend  
170 from a precursor protein called pro-peptide obtained from the cleavage of a signal peptide, a pro-  
171 prepeptide modified by C-terminal amidation, in the endoplasmic reticulum. The pro-peptide then  
172 undergoes multiple modifications, such as glycosylation and proteolytic cleavage, when passing the  
173 secretory route through the Golgi apparatus. The peptide is then transported through the dense core  
174 vesicles where, in addition to proteolytic cleavage, C-terminal cleavage and C-terminal amidation  
175 occur for some peptides. The vesicles, now full of accumulated peptides, are transported from the  
176 cell body down the axon. Upon stimulation, depolarization or other signals, the neuropeptides are  
177 then released by calcium-dependent exocytosis [26, 27].

178 Once released by neurons, neuropeptides can act on different cell and tissue types inside and outside  
179 the brain, such as endocrine system, the blood, digestive system. Hence, their pleiotropic  
180 capabilities. They show multi-level effects on genes, cells, organism and even on behaviors.  
181 Interestingly, neuropeptides use volume transmission, a dispersion method independent from  
182 synaptic communication that allows them to diffuse from the neurons to large distances in the  
183 extracellular fluid and CSF. Volume transmission, as well as lack of neuropeptides reuptake, eases  
184 their travel across the brain into different organs, where they have several different effects. It's of  
185 great interest to note the difference between neuropeptides and peptides. Both are involved in the



186 paracrine, autocrine and endocrine signaling. They are both synthesized and released by the same  
187 enzymes but neuropeptides are discretely secreted by neurons.

188 Neuropeptides can have both neuroprotective and neurodegenerative effects. It's of great interest to  
189 study their neuroprotective effect and their further therapeutic properties in neurodegenerative  
190 diseases. It's also important to investigate the neurodegenerative effects of some neuropeptides, in  
191 hopes of using them as biomarkers in the diagnosis of early-stage neurodegeneration, which will  
192 help in applying all neuroprotective agents as early as possible to ameliorate the disease prognosis.

193 In this article, we overviewed the neuroprotective effects of many neuropeptides in PD like: orexin,  
194 opioids, angiotensin, vasoactive intestinal peptide (VIP), pituitary adenylate cyclase activating  
195 polypeptide (PACAP), Neuropeptide Y (NPY), somatostatin, galanin, norepinephrine,  
196 octadecaneuropeptide (ODN) and nerve growth hormone (VGF), a well as other peptides such as  
197 carnosine, selanx, kinin and gastrointestinal peptide (GIP) and pancreatic peptide (PP). We included  
198 studies on neuropeptides that are equal or smaller than 100 amino acids, and published between  
199 2008 to June 2021. We investigated their effects on DA neuronal loss, inflammation, oxidative stress  
200 and apoptosis on the cellular levels in different animal models of PD and in PD patients from  
201 different biological samples. We also assessed the current state of neuropeptide' application on  
202 these PD models which endeavor to find their effects on behavioral, cognitive and motor functions.  
203 We aimed to present a solid basis that supports the use of neuropeptides as future therapies for PD.

204 A summary table classifying studies by location of neuropeptide's effect in PD and/or  
205 neuropeptide's level in different locations is shown below. The major findings regarding cellular  
206 effect (oxidative stress, inflammation, astrogliosis), motor dysfunctions, sleep disturbances and  
207 cognitive/memory impairment are presented (+ signified increased; – signified decreased).

Study	Peptide	Location	Levels in PD	Cellular effect	Motor impairment	Sleep deficits	Cognitive/memory impairment
Huang <i>et al.</i> 2021	Orexin-A	Plasma	+ in plasma Orexin-A levels (early-stage and medium-stage PD) – (advanced-stage PD)			+ in REM sleep	– in cognitive dysfunction
Stanojlovic, Pallais and Kotz 2021	Orexin	Lateral hypothalamus			+ exploratory locomotion & spontaneous physical activity	–	
Stanojlovic, Pallais, Lee <i>et al.</i> 2019	Orexin-A	Hippocampus		No effect on inflammation and astrogliosis			– hippocampus-dependent memory impairment
Stanojlovic, Pallais, Yllescas <i>et al.</i> 2019	Orexin-A	Medial prefrontal cortex					– social cognition impairment
Hadadianpour <i>et al.</i> 2017)	Orexin-A	CSF			+ locomotor activity + ability to hold wire		
Wienecke <i>et al.</i> 2012	Hypocretin (Orexin)	CSF	– over time in advanced stage PD			No association	
Xue <i>et al.</i> 2016	Orexin-A	Globus pallidus			+ body swing test		
Drouot <i>et al.</i> 2011	Orexin-A/hypocretin-1	Ventricular CSF	– over time in late-stage PD			No association	
Compta <i>et al.</i> 2009	Orexin-A/hypocretin-2	CSF	No difference				No association
Bridoux <i>et al.</i> 2013	Orexin-A	CSF				+ correlation between Orexin-A and REM epochs without atonia	
Stanojlovic, Pallais, and Kotz 2019	Orexin-A	Hippocampus and motor cortex			+ distance covered in locomotion test		
Giancola <i>et al.</i> 2017	VIP	Submucosal neurons	– of submucosal neurons containing VIP – due to $\alpha$ -syn overexpression				
Yelkenli <i>et al.</i> 2016	VIP	CSF		– GAD astrocytes	+ motor activity		

<b>Yu et al. 2020</b>	VIP and PACAP	Striatum		+ oxidative stress – inflammation – neuronal death	+ suspension test score
<b>Olson et al. 2015</b>	VIP	Substantia nigra		– inflammation + surviving dopaminergic neurons – microgliosis	
<b>Tunçel et al. 2012</b>	VIP	Striatum		– oxidative stress – apoptosis – NO levels	
<b>Korkmaz et al. 2012</b>	VIP	Striatum and SNpc		– neuronal death	
<b>Mosley et al. 2019</b>	VIP	SN		– inflammation – neuronal death VIPR2 agonist protects from $\alpha$ -syn induced inflammation, degeneration	
<b>Korkmaz et al. 2010</b>	VIP	CSF		+ NGF	
<b>Federoff, 2009</b>	NURR 1 and VIP		– due to $\alpha$ -syn overexpression	– expression of DAT due to NulP – VIP mRNA in embryos with loss of Nurrl function	
<b>Gao et al. 2017</b>	Angiotensin	SN	+	+ apoptosis + oxidative stress	
<b>Villar-Cheda et al. 2010</b>	Angiotensin	SN striatum		+ oxidative stress in SN & striatum	
<b>Rocha et al. 2016</b>	Angiotensin	Plasma	–		+ cognitive dysfunction
<b>Villar-Cheda et al. 2012</b>	Angiotensin II		+	+ oxidative stress + inflammation + neuronal death	
<b>Rodriguez-Pallares et al. 2012</b>	Angiotensin II			+ inflammation + neuronal death	

<b>Kubota et al. 2020</b>	Carnosine	Hypothalamus		- neuronal death - inflammatory response - ROS production		
<b>Bermúdez, Seroogy, and Genter, 2019</b>	Carnosine	In vivo and cells			- progression of motor deficits	
<b>Bermúdez, Skelton, and Genter, 2018</b>	Carnosine			- oxidative stress - inflammation		
<b>Maasz et al. 2017</b>	PACAP	CNS of snail SN of rats		- DA loss - alpha-syn and Lewy bodies (through PARK7)	-	
<b>Yu et al. 2020</b>	PACAP	Striatum			+ oxidative stress - inflammation - neuronal death	+ suspension test score
<b>Shivers et al. 2014</b>	PACAP	Striatum		- neuronal loss	- motor deficits	
<b>Brown et al. 2014</b>	PACAP	Culture in toxic THP-1 cells medium		- inflammation - neuronal death		
<b>Jouve et al. 2010</b>	Pronkephaline	Striatum	+ in PD, - after treatment			
<b>Sun et al. 2011</b>	Enkephalin			- oxidative stress - neuronal loss		
<b>Vinuela et al. 2008</b>	Enkephalin	Striatum	+ in PD, - after treatment			
<b>Ljungdahl et al. 2011</b>	Dynorphin	SN	+			+ dyskinesia
<b>Hanrieder et al. 2011</b>	Dynorphin	Striatum	+			
<b>Elson et al. 2018</b>	Galanin	Pedunculopontine nucleus	+	+ neuronal loss		
<b>Niewiarowska-Sendo et al. 2016</b>	Bradykinin			+ apoptotic processes + ROS release + NO release		
<b>Lazarova et al. 2018</b>	Neurotensin	Striatum		+ DA levels	- fall time	+ time to enter dark room
<b>Umehara et al. 2018</b>	Norepinephrine	Plasma				+ cognition
<b>Pain et al. 2019</b>	Neuropeptide Y	Striatum and SN		- inflammation		
<b>Decressac et al. 2012</b>	Neuropeptide Y	SNpc, striatum		- cell death - nigral dopamine neurons		
<b>Escamilla-Sevilla et al. 2011</b>	Neuropeptide Y	Plasma	+ over time			
<b>Bahdoudi et al. 2018</b>	Octadecaneuropeptide	Striatum and SN nigral tissues and ventral tegmental area		- neuronal degeneration - inflammation - apoptosis		
<b>Knudsen et al. 2017</b>	Pancreatic Polypeptide	Plasma	- in PD over time			
<b>Slominsky et al. 2017</b>	Semax	SNpc	+		No effect	+ anxiety
<b>Shiraishi et al. 2010</b>	Somatostatin	Plasma	+			

210

211

212

## 213 4.1. Orexin

214 Orexin was discovered in 1998 by Sakurai *et al.*, gets its name from orexis, Greek word for  
215 "appetite" [28]. It's also known as hypocretin, due to its expression in the posterior hypothalamus  
216 [29]. Orexin is neuropeptide mostly abundant in the neurons of the perifornical area of the lateral  
217 hypothalamus (LH). Orexinergic neurons send excitatory projections to arousal promoting areas in

218 the brain stem such as the locus coeruleus (LC) and the dorsal raphe (DR) nuclei involved in  
219 increasing wakefulness and vigilance state [30]. Alongside its important role in the circadian  
220 rhythm, orexin is also involved in promoting feeding via stimulation of the arcuate nucleus (Arc)  
221 and ventromedial hypothalamic nucleus (VMH), promoting energy expenditure via interaction with  
222 the brown adipose tissue and involved in neuroendocrine responses via projections to the pituitary  
223 gland. Indirectly, orexin activates the reward system by its projections to the ventral tegmental area  
224 (VTA) [8],[31].

225 Orexin has two homologous molecular forms: orexin-A and orexin-B, both derived from the same  
226 precursor peptide (prepro-orexin) [32]. Orexin A and B exert their various functions by binding and  
227 activating two G-protein-coupled receptors (GPCRs) called Orexin receptor 1 (OX1R) and Orexin  
228 receptor 2 (OX2R). OX1R is selective to orexin-A, binds to it with great affinity, however, OXR2  
229 is selective and binds to both orexins [33].

230 Recent studies are showing the involvement of the orexin/receptor system in important  
231 physiological processes of the brain such as sleep-wake cycle, as well as in pathophysiological  
232 processes of several neurological disorders [33]. Orexin or hypocretin deficiency is the main cause  
233 of human narcolepsy [34]. It has also been found reduced in neuromuscular disorders like myotonic  
234 dystrophy and in immune-mediated diseases like Multiple Sclerosis (MS). Most interestingly,  
235 orexin has been involved in several neurodegenerative disorders such as Alzheimer's disease and  
236 PD, which is of great interest to this review [35].

237 Significant differences in the levels of orexin-A have been found in the CSF of late-stage PD  
238 patients. Both CSF and plasma studies in PD showed a decreasing trend in orexin levels with the  
239 increasing severity of the PD, as measured by the Unified Parkinson's Disease Rating Scale Part III  
240 (UPDRS III) [36,37]. Drourot *et al.* also found further decrease in CSF orexins levels in a  
241 longitudinal study for 4 and 5 years in 2 PD patients [37]. This negative correlation, shows the  
242 progressive neurodegeneration of orexinergic neurons over time in PD patients [38]. However,  
243 another study reported unchanged levels of orexin in CSF [39]. The decreased CSF levels of  
244 orexin/hypocretin don't necessarily reflect direct correlation with the loss of orexin cells in the  
245 hypothalamus, as some orexinergic neurons might compensate for the neuronal loss by increasing  
246 the levels of orexin in the CSF [40]. Additionally, in PD the BBB becomes more permeable,  
247 allowing leakage of orexin/hypocretin in the blood [36]. As lumbar CSF and Plasma levels don't

248 reflect accurately the orexinergic loss in the LH in PD's brain, other tools could be used to assess  
249 the levels of orexin in PD and its reflection on degeneration.

250 Orexin plays a major role in the sleep/wake cycle. It has been shown to contribute to excessive day  
251 time sleep (EDS) in advanced PD [37],[41]. Dopaminergic neuronal loss in advanced PD did not  
252 correlate with EDS, and early-stage PD didn't majorly affect sleep. Interestingly, in an  
253 electrophysiologically controlled prospective study, sleep measures of nocturnal sleep, deep sleep,  
254 sleep architecture and efficiency, as well as EDS are all most significantly disrupted in advanced  
255 PD, where the orexin/hypocretin neuronal loss is most abundant [41]. Therefore, orexin  
256 neurodegeneration promotes sleep in advanced PD. PD treatment with dopamine agonist  
257 replacement therapy in 4 PD patients with sleep attacks showed decreased orexin levels in  
258 correlation with increased sleep attacks, suggesting the implication of orexin in reward circuit [42].  
259 On the contrary, Bridoux *et al.* found an increase in CSF orexin-A levels that correlated positively  
260 with epochs of rapid eye movement (REM) sleep without atonia, in patients during deep brain  
261 stimulation who underwent full night polysomnography pre surgery. In fact, orexin is therefore  
262 involved in the loss of REM atonia, implicating the involvement of orexin in REM behavioral  
263 disorder. Moreover, this study had a small sample size of 8 patients, where only 4 showed the  
264 significant correlation. It also lacked a control group, alongside the limitations electromyography  
265 technique imposes [43].

266 An increasing body of evidence is recently studying the relationship between orexin and motor  
267 activity in PD. The administration of orexin in the intraventricular CSF and globus pallidus (GP) in  
268 6-OHDA mice models of PD has shown its promising effects in improving locomotor activity and  
269 muscles weakness [44,45]. Hanging and rotarod tests following the administration of orexin,  
270 showed an increased time on rod and latency to fall [44]. Also, elevated body swing test post orexin  
271 administration resulted in rotation in the direction contralateral to the lesioned side [45]. On the  
272 other hand, orexin increased the firing rate of the GP neurons via ORX1 and ORX2 receptors in  
273 both ODHA and MPTP mice models of PD [45,46]. Orexin-A and B increased significantly the  
274 firing rate as recorded by the *in vivo* single unit electrophysiological recording, probably via their  
275 action on the Ca<sup>2+</sup> influx through the L-type Ca<sup>2+</sup> channel [46]. Xue *et al.* showed that orexin-A  
276 increases the firing rate of the GP via its action on the OX1R and OX2R [45]. Therefore, orexin  
277 achieves its therapeutic effects on motor symptoms via the activation of the GP, leading to the

278 inhibition the STN activity and therefore disinhibiting the thalamus, allowing the motor signal to  
279 pass from the motor cortex to the muscles, improving the posture and motor behaviors [46].  
280 However, the activation of the external and the internal GP, although both GABAergic neurons,  
281 have opposing effects on motor activity. The external one is implicated in the activation of motor  
282 neurons by inhibition of the STN. The internal GP inhibits the thalamus and therefore the voluntary  
283 movement [47]. Other studied reported the increased firing rate of the internal GP neurons and the  
284 STN in health rats [48,49]. The present finding proves the implication of orexin activation in  
285 pathophysiology of PD. However, its precise action on both the external and internal GP and STN  
286 need to be further studied.

287 Orexin alleviate motor deficits by its projections from the LH to other motor structures like the  
288 cerebellum and vestibular nucleus [50]. Inhibition of the orexinergic neurons, using designer  
289 receptors exclusively activated by designer drugs (DREADD) approach, has shown decreased the  
290 locomotor functions, energy expenditures and body composition as shown by the open field test ,  
291 calorimetry assessment of energy expenditures and spontaneous physical activity in A53-T mice  
292 models of PD [51,52]. In fact, orexinergic neurons recruit glutamic acid decarboxylase 65kD  
293 (GAD65) cells in the LH implicated in voluntary motor control. Hence, its inhibition, reduces the  
294 overactivation of GAD64 and the locomotor activity as quantified using treadmill rotarod testing  
295 [53].

296 It was also displayed, that orexin activation via DREADDS improves hippocampal memory  
297 impairment and social memory [54,55]. Activation of orexin by using DREADDS or by injecting it  
298 in the hippocampus, ameliorated the hippocampal dependent memory impairment as seen by the  
299 increased the latency to escape the Barnes maze and increased the total exploration time in the  
300 contextual object recognition test in 3, 5 and 7 months of A52T mice of models of PD [54]. The  
301 administration of orexin/hypocretin significantly restored social memory in PD model, during the  
302 automated two-enclosure homecage social test, that testes for sociability and social novelty (56).  
303 It's possible that orexin/hypocretin consolidates the social memory via its direct projection to the  
304 hippocampus or indirectly through the medial septum, through enhancement of synaptic plasticity  
305 and the modulation of the cyclic adenosine monophosphate (cAMP) response element-binding  
306 protein phosphorylation [54],[56]. Orexin is also a critical molecule in the execution of alertness  
307 and arousal. Stanojlovic *et al.* reported increased anxiety and social cognition after activation of

308 orexin neurons in the LH and the medial prefrontal cortex (mPFC) reciprocally [36],[52],[55]. The  
309 LH, the hippocampus and the mPFC are all part of the reward system in the brain. Orexin could  
310 have restored anxiety and social cognition by modulating the firing rate in any of these structures  
311 [52].

## 312 **4.2. Opioids**

313 Endogenous opioids peptides are a class of molecules that are synthesized in the brain and can act  
314 locally or circulate for more widespread systemic action. They are termed opioids for their  
315 presumed or confirmed binding to an opioid receptor in brain tissue [57]. Opioids peptides are a  
316 product of larger opioids precursors cleavage categorized into 3 families of molecules: enkephalin,  
317 dynorphin and endorphin. Met-enkephalins and leu-enkephalins are end-products of  
318 preproenkephalin (PPE or PPE-A) cleavage the precursor belonging to the enkephalins family.  
319 Similarly, prodynorphin (Pdyn or PPE-B) of the dynorphins family is cleaved to yield dynorphin-A,  
320 dynorphin-B and  $\alpha$  or  $\beta$  neodynorphin. Lastly, pro-opiomelanocortin belonging to the endorphins  
321 family is cleaved to yield melanocyte-stimulating hormone (MSH), adrenocorticotrophic hormone  
322 (ACTH)  $\beta$ -lipoproteins and  $\beta$ -endorphins [58,59].

323 After their secretion by a neuron, opioids peptides undergo enzymatic inactivation or transformation  
324 to stop or regulate their action on opioid receptors. Most dynorphins are later cleaved to Leu-enk-  
325 arg which is the end product of dynorphins transformation while the removal of tyrosine of  
326 dynorphins peptides usually deactivates their action on opioids receptors [59]. Classical opioids  
327 peptides receptors are a family of three receptors termed Kappa opioids receptor (KOPR), mu  
328 opioids receptors (MOPR) and delta opioids receptors (DOPR)[60]. Opioids have different affinities  
329 to opioids receptors depending on their type: dynorphin-B has a higher affinity to KOPR and  $\alpha$ -  
330 neodynorphin has no preferred affinity. Besides, opioid dynamics play a major role in receptor  
331 affinity as such, dynorphin-B, has higher KOPR affinity but leu-enk-arg has higher DOPR affinity  
332 [59]. Understanding opioids' nature and dynamics are very important to unravel their role and action  
333 in the healthy and the pathological brain.

334 Opioids in general are extremely important in brain activity and homeostasis through their action as  
335 neurotransmitters and neuromodulators to regulate different behavior and functions such as pain,  
336 memory, addiction, and many more. Consequently, a disruption in this system will likely cause



337 many physiological responses and malfunctions [61]. Disruption in opioid functions is non-avoidable  
338 in PD as opioid modulators are involved in the basal ganglia circuitry the center of PD  
339 pathophysiology: dynorphin is involved in the direct pathway while enkephalin is specialized in the  
340 indirect pathway making changes in their expression a likely outcome in PD [62]. As such, early  
341 studies regarding opioids in PD revealed an increase of enkephalin expression in the striatum with  
342 an increase in the GP in MPTP mice and marmosets reinforcing opioids involvement in PD  
343 pathophysiology [63]. Nowadays, there's an increasing line of evidence suggesting the involvement  
344 of opioids in L-dopa induced dyskinesia (LID) an involuntary movement of the face, limbs, or trunk  
345 caused by L-dopa administration [64].

346 Imaging mass spectrometry revealed dynorphin-B,  $\alpha$ -neodynorphin leu-enk-arg (resulting from  
347 dynorphin-B degradation and non-other) were increased in SN of highly dyskinetic 6-OHDA rats in  
348 comparison to their no or low dyskinetic counterpart. The degree of dyskinesia was assessed by  
349 blind observation of limb dyskinesia, mouth and tongue movement, axial dystonia, and rotational  
350 behavior. This increase in peptide levels was correlated with higher dyskinetic scores [59]. In a  
351 similar study assessing opioids levels in the striatum of unilaterally 6-OHDA lesioned rats,  
352 dynorphin-B and  $\alpha$ -neodynorphin were also increased showing similar correlative trends with  
353 dyskinetic scores [65].

354 Multiplexing ion mass spectrometry images of dynorphin-B and leu-enk-arg in the SN of highly  
355 dyskinetic mice revealed that the latter can only result of biodegradation of dynorphin-B. This  
356 enzymatic conversion of dynorphin-B to Leu-enk-arg is of great interest, as it shifts opioid receptor  
357 affinity from KOPR to DOTR/MOTR in the SN. This receptor affinity switch could have a major  
358 implication in dyskinesia pathology in PD and it's fortified by the concomitant increase in  $\alpha$ -  
359 neodynorphin that can bind all receptors [59]. Indeed nalbuphine, a KOPR agonist and MOPR  
360 antagonist, was found to be a good anti-LID agent in the primate model of PD [66].

361 Dyskinesia can be explained as long-term potentiation (LTP) of striatal N-methyl-D-aspartate  
362 (NMDA) receptors after L-dopa administration. Therefore, there is a link between over-excitation  
363 of the striatum by L-dopa with NMDA receptor and DA receptors. This LTP does not depotentiate  
364 causing the motor complications of LID [67]. Interestingly, Des-dynorphin can bind to NMDA  
365 receptors possibly exhibiting an inhibitory effect on the striatum. As such, the Des-tyrosin-

366 dynorphin increase in the striatum could be implicated in a compensatory mechanism to alleviate  
367 striatal overstimulation of D1 receptor by unregulated L-dopa activity of L-dopa drugs [65].

368 Lucia Frau *et al.* found that the first movement after denervation of 6-OHDA rats induced by  
369 dopamine agonism could be responsible for dyskinetic features and symptoms in these PD rat  
370 models. Consequently, prohibiting rats from executing movement after apomorphine stimulation by  
371 placing them in a restrainer significantly reduced dyskinesia *vs* rats placed in hemispherical bowls  
372 where the movement was possible as measured by contralateral movement behavior. Using *in situ*  
373 hybridization, mRNA levels of the transcription factor zif-268 were differentially increased in  
374 dynorphin + striatal cells of freely moving mice after stimulation with SKF 38393, a D1 agonist,  
375 hinting at a change in molecular gene expression of dynorphin neurons following L-dopa agonism  
376 in this “priming model” of PD dyskinesia [68].

377 Following dynorphin’s trends enkephalins peptides were increased in the striatum of 6-OHDA  
378 dyskinetic rats in L-dopa treated side *vs* saline treated side as measured by Nilsson *et al.* using  
379 quantitative mass spectrometry [69]. Besides, in a study done by Jouve *et al.* 2010, *in situ*  
380 hybridization revealed that PPE mRNA levels were elevated in the striatum of 6-OHDA rat escorted  
381 by worsening of sensimotor and motor functions measured by corridor task and cylinder test  
382 respectively as well as increased forelimb dyskinesia. Consequently, sub-chronic high-frequency  
383 stimulation of the thalamic centromedian-parafascicular complex was able to reduce the PPE mRNA  
384 level elevation, thus normalizing motor dysfunctions and partially reducing dyskinesia [70].  
385 Paralleled, PPE RNA leveled normalization was found in an attempt of grafting ventral  
386 mesencephalic cells from wild-type or DAT kappa opioids (KO) in 6-OHDA mice model with  
387 dyskinesia assessed by blinded observation of abnormal involuntary movements. Wild-type  
388 transplantation was found to be better at alleviating dyskinesia and showed less diffuse extra and  
389 intracellular DA levels assessed with high-pressure liquid chromatography [67]. Taken together,  
390 these findings reinforce enkephalin implication in PD and overall opioids role in LID with a close  
391 association with L-dopa regulation and administration. An interesting study on restless leg  
392 syndrome found that delta-opioid agonist D-Ala2, D-Leu5-enkephalin (DADLE) was able to protect  
393 DA neurons *in vitro* against iron deficiency which is related to ROS formation and DA neuron  
394 degeneration. Although, opioid implication in PD is complex making the need for *in vivo* testing to  
395 assess DADLE’s significance in PD [70,71].

396 Lastly, we should mention the possible implication of a rather newly discovered opioid peptide  
397 called orpahn FQ or nociceptin (OFQ/N). OFQ/N is a rat neuropeptide involved in the indirect  
398 striatum/thalamus pathway. When activated in PD, it increases the secretion of OFQ from the  
399 subthalamic nucleus's glutamatergic terminal nerves, or by the reduction GABAergic activation  
400 from the SN [79]. Hence, the increased OFQ expression in the SNC pars reticulata, SNpc and the  
401 subthalamic nucleus, as well as in the CSF of PD patients [80].

### 402 ***4.3. Vasoactive Intestinal Neuropeptide***

403 VIP is neuropeptide, made of 28 amino acids, secreted in the central and peripheral nervous system  
404 [73]. As its name suggests, VIP was initially discovered in the intestine of the hog [74]. It also plays  
405 an important role as an immunoregulatory neuropeptide, produced by lymphocytes T and B cells,  
406 also by mast cells and eosinophils stimulated by cytokines like interleukin (IL)-6, and IL-1 $\beta$  [75].  
407 VIP has numerous and diverse biological functions such as respiratory stimulation, hypotension,  
408 vasodilation and hyperglycemia [74]. It's involved in the digestive system as a regulator of smooth  
409 muscle contraction and epithelial secretion and blood flow. VIP downregulation is associated with  
410 chronic constipation in PD patients [76]. Due to its various functions, VIP is produced in the  
411 central and peripheral system by neurons, in the endocrine system by glands and in the immune  
412 system by immune cells and nodes, as well as in the heart, the lungs, the kidneys, the thyroid  
413 glands, the gastrointestinal (GI) tracts [73]. VIP is a member of the secretin (a peptide hormone  
414 composed of 27 amino acids) receptor family with related structure that includes growth hormone  
415 releasing hormone (GHRH), glucan, glucagon like peptides and PACAP. Due to their homologous  
416 amino acids sequences, both VIP and PACAP share 3 GPCR: PAC1-receptor (PAC1-R), the  
417 VPAC1-receptor (VPAC1-R) and VPAC2-receptor (VPAC2-R) [77].

418 The hallmark of PD must be the neurodegeneration of dopaminergic neurons in the SNpc, that  
419 disrupts the direct and indirect pathway from the striatum to the motor cortex, inducing impaired  
420 motor skills [47]. VIP has proved its neuroprotective function in PD, by increasing neuronal cells  
421 viability, decreasing dopaminergic neuronal loss and promoting the activity of DAT [77,78]. In 6-  
422 OHDA parkinsonian rats, VIP was capable of protecting not only the neurons but also the myelin  
423 sheath and reverse the motor defects [80]. Tunçel *et al.* reported direct evidence on VIP anti-  
424 apoptotic and anti-oxidant properties, as shown by the decreased DNA fragmentation and lipid  
425 peroxidation respectively. It also regulated the levels of the first line antioxidant defense system:

426 superoxide dismutase (SOD) and catalase (CAT) that were found disrupted in PD mice model [78].  
427 Golgi-Cox staining and stereological methods were used, respectively, to determine the  
428 morphological densitretic changes occurring in the neurons of the striatum and their number in the  
429 SNpc in 6-OHDA PD rat model. The intra peritoneal administration of VIP showed its effects on  
430 restoring the density of the striatal dendritic spines and the number of dopaminergic neurons  
431 reduction in PD [79, 80].

432 VIP once released in the body, can cross the BBB into the CNS. However, due its short half-life, its  
433 rapidly metabolized and cleared out. Therefore, limiting its potential use as therapeutic candidate  
434 for PD [80, 81]. Hence why several studies are tagging TAT, a cationic Arginine-rich peptide  
435 (CARP), to VIP in hopes of increasing its potency and traversing capabilities. Only VIP-TAT  
436 enhanced the motor deficits, increased the levels of DA and its metabolites (levodopa (L-dopa) and  
437 homovanilic acid (HVAC)) and SOD levels in MPTP mice model of PD when compared to VIP,  
438 using the pole-climbing and Paws suspension test, the liquid chromatography mass spectrometry  
439 analysis system, and the antioxidative activity SOD evaluation kit in the striatum reciprocally. The  
440 improved neuroprotective effects are mostly caused by the enhanced potency of VIP-TAT and  
441 affinity to activate PAC1-R. The electrostatic interaction between the catatonic TAT domain and  
442 the anionic PAM (positive allosteric modulation) domain of the extracellular domain of PAC1-R  
443 (PAC1-EC1) induces conformational changes in PAC1-EC1 that results in the interaction between  
444 the PAC1-R and VIP-TAT necessary to its activation [79]. The activation of PAC1-R contributes to  
445 the activation of the CARP mechanisms and the extracellular signal-regulated kinases (ERK)  
446 pathway, that promote neuroprotection against PD pathophysiology [78],[82].

447 In another approach to use VIP as a drug to target PD, VIP-receptor 1 and VIP-receptor 2  
448 antagonists, LB 3393 and LBT-3627, neuroprotective properties have been investigated. Treatment  
449 with LBT-3627 gives rise to a link between the neuroprotection and the adaptive immune response  
450 [82]. This VIP-receptor 2 antagonist is an effective modulator of PD pathophysiology, as it  
451 decreased in a dose dependent manner the dopaminergic loss, reduced the reactive microglia's  
452 levels and decreased the expression of genes associated with pro-inflammation and oxidative stress  
453 in CD11+ cells (microglia). Interestingly, in a MPTP models of PD, LBT-3627 treatment elicits  
454 immunosuppressive effects on adaptive immunity where it increased inhibition of responder T cells  
455 by regulatory T cells, improved the activity of Tregs, as well as inhibited the production of

456 proinflammatory cytokines by helper T cells. Therefore, LBT-3627 modulation of the adaptive  
457 response association with inflammation by creating a shift from pro-inflammation towards anti-  
458 inflammation and ultimately neuroprotection. A cross-talk between the CD4+ T cells and the CD11  
459 microglia cells could have taken place in creating the link between immuno-suppression and  
460 neuroprotection [81],[83].

461 Moreover, the motor deficits in PD have been linked the GABA neurotransmitter. VIP recovered  
462 the motor deficits by increasing GABA levels in the ventral anterior nucleus of the thalamus  
463 (VATH), as well as in the neurons of the striatum without modulating the dopamine turnover  
464 [84,85]. In 6-OHDA brain slices of the VATH from rat model of PD, immunohistological staining  
465 showed that the administration of VIP at 25 ng/KG is capable of restoring the levels of GABA and  
466 the number of nerve growth factor (NGF) and the rat mast cell protease II (RMCPII) -  
467 immunoreactive mast cells in the thalamus of PD models [84].

468 Interesting, Federoff *et al.* describes PD as a developmental disorder. NuIP, the Nurr1 (nuclear  
469 receptor 1) interacting protein, a modulator of DA phenotype has a crucial role in the survival of  
470 DA neurons during the brain development. It stimulated the transcription of Nurr1 which in turn  
471 induces the expression of DA proteins (DAT and TH) and enhances VIP production. VIP in turn  
472 activates neurotrophic factors necessary for DA survival and microglia as immune-suppressor in the  
473 CNS. Therefore, insuring DA survival and function [87]. However, environmental modulators and  
474 increase in  $\alpha$ -synuclein the CNS might downregulate NuIP during development resulting in loss of  
475 DA neurons and PD pathology [86, 87].

#### 476 **4.4. Angiotensin**

477 Two independent renin-angiotensin-systems (RAS) exist in the human organism: the circulating  
478 cardiovascular hormonal system and the brain RAS [89]. Hormonal RAS regulates the blood  
479 pressure, the sodium homeostasis and the volume of body fluids, by enhancing the reabsorption of  
480 water and sodium. Renin is secreted in the afferent arteria of the kidney. Once released, renin  
481 cleaves angiotensinogen, found circulating in the plasma and secreted by the liver, into the inactive  
482 precursor angiotensin I. Angiotensin-converting enzyme (ACE) converts the latter into the leading  
483 effector of the RAS: angiotensin II (AII) [90]. In the brain, AII is mostly secreted by glial cells (i.e  
484 microglia, astrocytes, and oligodendrocytes) in regions responsible of cardiovascular functions and

485 other brain regions (hypothalamus, etc...) where it plays an important role in memory, anxiety,  
486 bipolar disorder and especially in PD [88],[90].

487 Angiotensin receptors type 1 and type 2, AT1R and AT2R , are located in different regions in the  
488 brain and along the spinal cord [91]. AT1R is expressed in the CNS by astrocytes, microglia and  
489 even by neurons in particularly DA neurons. AT1 isn't only expressed in the membrane of the cells  
490 but also intracellularly in the nuclei membrane, inside the nuclei and in the membranes of the  
491 endoplasmic reticulum [92]. The AII/AT1R axis induce a pro-inflammatory and pro-oxidative states  
492 by production of ROS and activation of nicotinamide adenine dinucleotide phosphate (NADPH)  
493 complex. Its overactivation induces harmful effects upon the brain: neurotoxicity,  
494 neuroinflammation, as well as facilitated release of DA in the CNS. Interestingly, it exerts  
495 inhibitory effects on GABA and excitatory effects on glutamate, therefore decreasing GABA and  
496 increasing glutamate release, which suggest an important role of AT1R activation in the indirect  
497 pathway of the SN, especially in motor deficits in PD. As opposed to AT1R functions, AII/AT2R  
498 activation yields neuroprotective effects in the brain. AT2R activates nitric oxid (NO) production,  
499 enhances neurite outgrowth and improves memory learning and cognition [93]. Decreased levels of  
500 AII, measured using the ELISA test, is associated with increased severity of depression symptoms  
501 in thirty PD patients [94]. Hence why the study of RAS in PD is of major interest.

502 The AII/AT1R axis triggers dopaminergic neuronal loss, especially in the SN as seen by the  
503 reduction in 70% of tyrosine hydroxylase neurons due to AII administration and restored with  
504 candesartan (AII inhibitor), in rotenone, MPTP and 6-OHDA PD mice models [94-96]. A  
505 multifactorial mechanism seems to be at the base of the pro-apoptotic activity of AT1R in  
506 dopaminergic cells: via NADPH mediated oxidative stress or via mitochondrial apoptotic signaling  
507 [95]. In different PD models, in the DA neurons of the SN, AII enhanced the expression mRNA and  
508 protein AT1 receptor and induced its overactivation. AT1R activates mitogen-activated protein  
509 kinase (MAPK) cascade initiated by the protein kinase C (PKC), the critical actor of AT1R effects.  
510 PKC binds to and catalysis p47phox, therefore activating NADPH complex, the main source of  
511 ROS production in the cell [98]. In a more direct evidence, especially the activation of the  
512 intracellular NADPH-oxidase 4 (NOX4), induces the activation of the superoxide cascade, the  
513 overexpression of oxidized guanosine 8-OH guanosine, and activation of caspase-3, giving rise to  
514 DNA damage in DA neurons of PD model, and resulting in apoptosis of DA neurons [91],[94].

515 AII also stimulates ROS generation by activation of the intracellular mitochondria. A cross talk  
516 between cytosolic NADPH complex and mitochondrial ATP-sensitive potassium channels  
517 (mito(KATP)) exists where NADPH activates mito(KATP) oxidase production and the latter  
518 modulates the extramitochondrial oxidative stress. In DA neurons of PD mice models, the inhibition  
519 of mito(KATP) inhibits the DA neuronal loss, blocks the superoxide induced ROS and reduces the  
520 inner mitochondrial membrane potential induced by AII administration. All of which confirms the  
521 enhancing role of mito(KATP) on AII induced dopaminergic neurodegeneration [97].

522 Moreover, AT2R exerts its neuroprotective effects by decreasing the NADPH oxidative stress  
523 activation, therefore restoring the DA neurons in the SN [95],[97]. The opposing relationship  
524 between A1TR and A2TR has been extensively studied and shows a counterbalance between the  
525 action of the two receptors. AT1R induction of ROS is counteracted by activation of AT2R that  
526 decreases NADPH expression. Therefore, the unbalance between the activation of the two receptors  
527 towards an overly activate AT1R pathway may increase the risk of PD via enhanced oxidative  
528 stress production and increased DA neurodegeneration [97,98].

529 DA depletion exerts a counter regulatory effect on AT1R expression. In 6-OHDA mice model of  
530 PD, depleted DA neurons show increased AT1R expression [95-98]. However, in L-dopa presence  
531 its expression is reduced [98]. Adversely, in aging rats AT1R expression was found upregulated and  
532 AT2R expression is downregulated, which may lead to a pro-oxidative and pro-inflammatory state  
533 that increases dopaminergic neuron's vulnerability [99]. Hence, why it's important to question the  
534 following: does the neurodegeneration of DA neurons in PD lead to the dysfunction in AII/AT1R  
535 axis, in a manner where the AII/AT1R/NOX4 seeks to protect DA neurons and promote neuronal  
536 regeneration and resilience, but when the neuronal stress is extended over time the same mechanism  
537 induces oxidative stress and apoptosis [92]. Or, does the increase in AII/AT1R axis upregulation,  
538 due to normal aging, increase DA neuron's vulnerability and impose a risk factor for PD?

539 Labandeira-Garcia *et al.* suggested a double mechanism of action of AII on DA neurons and on  
540 microglia. In DA neurons, AII activates AT1R that induces NADPH NOX activation and produces  
541 low levels of ROS in the nuclei. In microglia cells, AII induces the release of high levels of ROS  
542 and superoxide-activated ROS, that damages of DA neurons. Microglial polarization is the shift  
543 from the M1, proinflammatory and death inducer, phenotype to the M2 , immunoregulatory and  
544 regenerative, phenotype in an inflammatory response [100]. It has been reported that microglia play

545 an important role in enhancing the effects of AII on ROS production in PD models, and inducing  
546 neurodegeneration [97]. As well as, interacting with the neuroprotective estrogen in the SN, that  
547 regulates AT1R post-transcriptional expression to reduce DA neuronal loss [96]. This suggests that  
548 the proinflammatory M1 microglia is activated by the AII/AT1R axis and the M2  
549 immunoregulatory microglia is activated by the AII/AT2R axis.

#### 550 **4.5. Carnosine**

551 Carnosine or ( $\beta$ -alanyl-L-histidine) is a dipeptide found in vertebrate's skeletal muscles and brains  
552 making animal dietary consumption of fish and meat one of its best sources [101]. Taken as a  
553 supplement for exercise with the aim of better physical performance, many other roles have been  
554 attributed to this peptide since its discovery in Russia in 1990. Indeed, this dipeptide is proven to  
555 have anti-oxidant and antiglycation properties as well as having a role in Cu and Zn chelation and  
556 wound healing promotion [100, 101]. Carnosine, as well as its precursors but to a lesser extent, is  
557 capable of crossing the blood-brain barrier making the use of exogenous carnosine in  
558 neuroprotection more applicable. Carnosine also exist in endogenous form. It is synthesized by  
559 muscle cells, oligodendrocytes and olfactory neurons and latter metabolized by carnosinase in the  
560 kidneys, liver, and serum [103].

561 Interest regarding carnosine neuroprotective effect is on the rise, carnosine additive administration  
562 has been found to alleviate disease-related symptoms better than classic therapy in PD patients in a  
563 controlled clinical trial done by Boldyrev *et al.* 2008 [104] as measured by UPDRS rating scale.  
564 Also, this dipeptide caused less behavioral and motor dysfunctions than DA alone in rat model  
565 when administered as a pharmacological compound with DA. These rats showed less locomotion  
566 depression and more entries and time spent in open zones [105]. Similarly, when carnosine was  
567 introduced intranasally in th1-asyn mice models, the latter showed less motor deficit compared to  
568 no treatment group as assessed using the challenging beam traversal test [106].

569 Carnosine can exhibit its protective effect by inhibiting ROS formation [103], [105, 106] through an  
570 enhancement of glutathione peroxidase (GPX) in a-syn mice model measured by RTPCR [108] and  
571 through SOD in MPTP and 6-OHDA rat models [104], [108] as revealed using superoxide  
572 dismutase (SOD) measuring assay. SOD and GPX are two enzymes involved in cellular oxidative  
573 stress resistance, thus an increase in SOD and GPX activity reinforces carnosine's role as an anti-



574 oxidant. Although this stress-related response seems to have a threshold for its activity as carnosine  
575 alone [105, 106] or in presence of low oxidative states [105] doesn't show this same effect.  
576 Consequently, western blot analysis showed that similar ROS inhibition by carnosine pre-treatment  
577 led to a down-regulation of stress-activated protein kinases (SAPK)/ Jun amino-terminal kinases  
578 (JNK) pathway of the MAPK family involved majorly in cell death and inflammation in 6-OHDA  
579 immortalized hypothalamic neuronal GT1-7 cells. In this case, carnosine successfully suppressed 6-  
580 OHDA induced upregulation of JNK. In the same cell line, carnosine also showed inhibition of  
581 integrated stress response genes such *Chop*, *Gadd34*, and *Atf4* further enhancing cell survivability  
582 as revealed by RT-PCR [107]. These 2 pathways, among others, could work hand in hand to exhibit  
583 neuroprotective effects by slowing down disease progression and onset through reduction of cellular  
584 oxidative state.

585 Carnosine plays a major role in protecting against neural inflammation. It has been found to reduce  
586 the activation of many pro-inflammatory cytokines induced by different PD models, such as IL-  
587 1 $\beta$ [106-108], IL-6 [107], [108] and MCP-1 [108]. As well as, tumor necrosis factor-alpha  
588 (*Tnfa*), cyclooxygenase 2 (*Cox2*), and toll-like receptor 4 (*Tlr4*) [107] as revealed using  
589 ELISA[106], [108] or RT-PCR [107] methods. Interestingly, carnosine administration has an  
590 inhibitory effect on INOS and NOS in MPTP mice two pro-inflammatory enzymes known to  
591 promote inflammatory interleukins production under *Tnfa* activation [108]. Using in silico method  
592 of upstream regulator analysis Bermudez *et al.* 2008 predicted and normalized Trem1 (trigerring  
593 receptor expressed on myeloid cells 1) activation in a-syn mouse models when treated with  
594 carnosine in drinkable water to be similar level of healthy controls [109]. Trem1 is an activator of  
595 tumour necrosis factor alpha (TNF- $\alpha$ ). Therefore Trem-1 activation of TNF- $\alpha$  leads to increased  
596 INOS and NOS enzymes activity through NF-kappa-B pathway and thus increasing anti-  
597 inflammatory cytokines [106],[108]. It would be interesting to further test carnosine's effect on this  
598 pathway to better understand the mode of action of carnosine in neural inflammation. Lastly,  
599 carnosine's effect is not limited to neural inflammation and ROS control as it was able to re-  
600 increase the expression of the mitochondria genes complexes I, IV and V after it was attenuated by  
601  $\alpha$ -synuclein overexpression in mice, therefore, increasing mitochondrial function and respiration  
602 [109].

603

604

#### 605 ***4.6. Pituitary adenylate cyclase-activating polypeptide***

606 PACAP is a 27- or 38-amino acid neuropeptide, belonging to the intestinal  
607 polypeptide/glucagon/secretin family [110]. This peptide exists in two forms termed and PACAP27  
608 (27 amino acids) and PACAP28 (28 amino acids) which is an N-terminal cleaved form of the latter.  
609 This peptide was discovered in 1989 in the ovine hypothalamus but since then, PACAP was also  
610 found in other brain regions such as the amygdala, the septum, the GP, the midbrain, and many  
611 others. PACAP can also be found in non-CNS tissues such as the digestive and respiratory systems  
612 [110, 111]. Studies regarding this peptide found that it has many roles like regulating insulin  
613 secretion and immunity. It also exhibits an anti-apoptotic effect and can promote cell proliferation  
614 [113]. Neural inflammation and apoptosis are well-documented pathophysiological hallmarks of PD  
615 [12]. Taking this into consideration many studies were interested in unraveling its possible  
616 implication in PD by protecting the dopaminergic cells from degeneration.

617 Indeed, PACAP seems to be effective at alleviating Parkinson-like symptoms and increasing  
618 survivability in animals. As such, it was able to increase the survivability of the rotenone snail  
619 model of PD concomitantly improving motor functions and feeding [114]. Similarly, PACAP  
620 reverted parkinsonian-like symptoms induced by prostaglandin injection in mice, MPTP in mice,  
621 and 6-OHDA in rats [113-115]. MPTP mice treated with PACAP showed higher pole climbing and  
622 suspension scores thus better coordination and motor function than untreated counterparts [115]. As  
623 to mice infused unilaterally with prostaglandins in the SN, they showed worse forelimb asymmetry  
624 and postural stability measured with cylinder test and curling test respectively. Co-injection of  
625 PACAP with prostaglandins normalized motor dysfunctions score to be comparable with healthy  
626 controls [116].

627 High pressure liquid chromatography analysis of neurotransmitters levels of PD animal models  
628 found that, although PACAP seems to be also capable of restoring DA striatal levels in 6-OHDA  
629 mice all while rescuing dopaminergic degeneration it was unable to restore dopamine levels in  
630 MTPP regardless of its positive effect on motor symptoms [115]. PACAP did not affect 5HT  
631 restoration in the striatum of 6-OHDA mice and in the Retonon snail model. Lastly, PACAP failed  
632 to inhibit microglial activation in PG-J2 (prostaglandin J2) mice. Co-administration of PACAP with

633 prostaglandins did not reduce the amount of IBA1+ cells in brain tissues of treated mice as assessed  
634 by immunostaining [113],[115].

635 PACAP shares 68% structural similarities with VIP. Therefore, VIP and PACAP share two GPCR,  
636 VPACR-1 and VPACR-2. PACAP can also specifically bind to its specific PAC-1 receptor found  
637 distributed in brain tissues but also in the SN [111]. There's growing evidence suggesting that  
638 PACAP exhibits its protective effect in PD through this receptor by inhibiting apoptosis. The  
639 downstream effect of PACAP activation of PAC-1 is the induction of adenylyl cyclase and later  
640 protein kinase A (PKA). PKA can have many effectors including the activation of cyclic AMP  
641 response element binding protein (CREB) which promotes brain-derived neurotrophic factor  
642 (BDNF) and inhibits caspase 3, therefore, promoting cell survival [113],[116]. Indeed, PACAP was  
643 successfully able to prevent neuroblastoma-derived cell line (SH-SY5Y) death expressing high  
644 levels of DA when introduced in the toxic medium of stimulated pro-inflammatory THP-1 cells.  
645 Western blot analysis of the surviving cells showed low lower levels of caspase 3 and a higher level  
646 of CREB and BDNF when co-administered in medium with PACAP but not when in presence of  
647 PAC-1 antagonist [117].

648 This pathway also explains why PACAP couldn't deactivate microglial activation in PG-j2 mice.  
649 PG-j2 acts through GPCR coupled with Gi protein to inhibit cAMP which can be countered by  
650 PACAP through PAC-1. Although PG-j2 can also bind protein on the sulfhydryl ramification  
651 causing chronic inflammation and proteins aggregation which may not be altered by using PACAP  
652 [117]. Another pathway of PACAP's action can be through PARK7 (protein coding gene associated  
653 with PD7) which was rescued by PACAP in 6-OHDA rats. PARK7 is a chaperon protein with anti-  
654 oxidant and anti-apoptotic properties. PARK 7 can also stop apodosis by inhibiting the proapoptotic  
655 protein-associated splicing factor (PSF). Besides, it could be involved in inhibiting ROS formation  
656 by stabilizing NRF2 (nuclear factor erythroid 2 related factor 2) protein, a regulator of anti-  
657 oxidative stress. PACAP's possible implication in oxidative stress is further supported by an  
658 elevated SOD level in MTP mice after its administration. Lastly, PARK7 can stop mutant  $\alpha$ -  
659 synuclein aggregation which is another important pathological hallmark of PD [113,114].

660 Briefly, PACAP seems to exhibit some neuroprotective effects through inhibition of apoptosis and  
661 oxidative stress *in vivo* and *in vitro* but the extent of its protection differs depending on animal

662 models. More *in vivo* studies should explore the molecular aspect of such discrepancies before  
663 studying its application in humans.

#### 664 **4.7. Other neuropeptides**

665 PD's most pathological characteristic is the presence of Lewy bodies, their fibrils are mostly made  
666 of  $\alpha$ -synuclein. Lewy bodies are widely distributed across the central and peripheral autonomic  
667 nervous systems including the enteric system, cardiac plexuses, adrenal gland, etc... [118]. It's  
668 especially found in the dorsal motor nucleus of the vagus nerves in the medulla oblongata. The  
669 secretion of both somatostatin and pancreatic polypeptide (PP) from the pancreas is controlled by  
670 the vagus nerve, which is why they're used as markers for vagal nerve integrity [119]. Somatostatin  
671 is known as a growth hormones inhibitor, and has various inhibitory effects on GI tract, endocrine  
672 and exocrine systems , as well as modulates neurotransmission and formation of memory in the  
673 CNS and most importantly has anti-proliferative effects [120]. On the other hand, PP is secreted by  
674 islet and acinar cells in the pancreas. Its major role is to regulate the pancreatic secretion, as well as  
675 modulate the contraction of the GI tract and gall bladder, hence its importance in regulating the  
676 digestive system that's disrupted in PD [121]. In fact, in the plasma of PD patients, somatostatin is  
677 upregulated and PP is downregulated. These results show the contribution of somatostatin in PD  
678 pathophysiology in the digestive system and PP involvement in the disrupted function of the GI  
679 tract found in PD [119], [122]. NPY has also been found increased in the plasma of PD patients  
680 undergoing deep brain stimulation [123]. The neuroprotective role of NPY in PD has been widely  
681 studied in both 6-OHDA PD mice models and *in vitro* with neuroblastoma cells. NPY has been  
682 shown to protect DA neurons and their terminals from cell loss, in both cells and mice PD models,  
683 in the SN and the striatum, via activation of their Y2 receptor specifically, elucidating its  
684 neuroprotective effects. It also showed significant results in restoring the expression of DAT and  
685 the concentration of DA and its metabolites. This neuroprotection might be mediated by the  
686 activation of ERK  $\frac{1}{2}$  and protein kinase B (AKT) pathways, or by the inhibition of the  
687 neuroinflammatory process elicited by the excessive activation of microglia. Blocking microglial  
688 activation, reduces apoptosis of DA neurons therefore alleviates the behavioral and motor  
689 impairments found in PD [124]. Interestingly, Apelin, a novel neuropeptide, is showing its  
690 regulating and neuroprotective effects on brain functions. In a 6-OHDA model of PD, motor  
691 assessment tests like accelerating rotarod, balance beam and beam traversal tests and the bar tests

692 showed significant motor improvement when lesioned rats were treated with increasing  
693 concentrations of Apelin-13. Not only Apelin decreased the motor impairment in PD rat models but  
694 also, increased the dopaminergic receptor's levels, attenuated the DA loss in the substantia nigra.  
695 The destruction of the dopaminergic pathway in the SN can affect the functioning of the striatum  
696 and therefore lead to a loss of its synaptic plasticity, which is represented by the loss of the  
697 membrane associated proteins such postsynaptic density protein 95 (PSD-95), neuroligin,  
698 neurexin1, metabotropic glutamate receptor (mGlu R1). The administration of Apelin-13  
699 significantly increased the expression of these proteins in the PD lesioned model, therefore  
700 protecting the synaptic plasticity in the striatum [124]. Octadecaneuropeptide (ODN) is a  
701 neuropeptide secreted extensively by astrocytes in the CNS. It also exerts neuroprotective action on  
702 dopaminergic neurons and astrocytes through preventing astrogliosis, oxidative stress and  
703 inflammation in the SNpc , the striatum and in the ventral tegmental area [125]. Emerging evidence  
704 is showing that the motor and non-motor symptoms occurring in PD are in fact, induced by  
705 degeneration in the cholinergic neurons rather than in the dopaminergic neurons alone [126]. The  
706 pedunculopontine nucleus (PPN), is extremely rich in cholinergic neurons and plays a major role in  
707 the regulation of movement execution, maintenance of arousal and awareness in posture and  
708 balance [127].

709 Galanin, is a neuropeptide distinguished from other peptides by its co-existence with  
710 neurotransmitters such as dopamine and acetylcholine. In a Lactacystin mice model of PD, galanin  
711 was increased in cholinergic neurons in PPN, especially near the side of the toxin injection. This  
712 upregulation marks the pro-survival, anti-inflammatory and anti-oxidative stress action of galanin  
713 towards the toxin. It might show the compensatory role of galanin, it compensates for the damage  
714 induces by the neurovegetative toxin to maintain movement and arousal as long as possible. Further  
715 studies need to demonstrate if the rise in galanin has significant change on motor impairment in PD  
716 and investigate its therapeutic properties [126]. Locomotor impairment has been reported reduced  
717 by analogues GIP in chronic PD mice models [128]. GIP or glucose-dependent insulinotropic  
718 polypeptide, secretion is essential to stimulate insulin release. It also has anti-apoptotic effects and  
719 induces growth [129]. Through the reduction of oxidative stress, astrogliosis, microglial activation,  
720 inhibition of the  $\alpha$ -synuclein expression as well as protection of dopamine synapses and  
721 mitochondrial activity, GIP exerts its anti-parkinsonian action on chronic PD, along with the  
722 increase in the BDNF expression to induce neuronal growth and fight neurodegeneration [128],

723 [130]. Several other neuropeptides have been found modified in PD patient's plasma, such as  
724 decreased VGF cleaved peptides and increased norepinephrine, and in 6-OHAD mice model of PD  
725 where selanx was found increased as a marker of anxiety [129-131]. Moreover, neuropeptides can  
726 also have neurodegenerative properties and induce parkinsonian motor and non-motor symptoms.  
727 A great example of toxicity enhancer is the kinin peptide: bradykinin. In a cellular model of PD,  
728 bradykinin not only activates pro-apoptotic pathways but also activates inflammatory response  
729 enhancing the release of cytokines by neurons: IL-1 $\beta$ , IL-6 and TNF- $\alpha$ , as well as activates the  
730 oxidative stress leading to casapase-3 activation. All of which inhibits cell survival, enhances DA  
731 neurons loss. However, if the activation of bradykinin is a consequence or a cause to PD  
732 pathophysiology is a matter that needs to be studied in further experiments [134]. The formation  
733 and release of neuropeptide vesicles are also impaired due to the endoplasmic reticulum lipids that  
734 create contact surfaces with mitochondrial membranes and induces morning anticipation deficits  
735 and increases awakening at night in drosophila model of PD. These results have been evolutionary  
736 conserved from drosophila to hypothalamic neuron in PD patients [135]. Deep brain stimulation is a  
737 therapeutic procedure used in PD to help alleviate the motor disorders patients experience. The  
738 connection between the brain-gut axis has led to investigating the effects of deep brain stimulation  
739 (DBS) on the secretion and concentration levels of several neuropeptides such as ghrelin, especially  
740 the acetylated ghrelin peptide produced in the stomach. Before the DBS in PD patients, a decrease  
741 in level of plasma acetyl ghrelin during fasting and postprandial. However, after the DBS procedure  
742 the PD patients showed an increase in this concentration. These results suggest an impairment in the  
743 normal functioning and secretion of ghrelin in the stomach. These results are of high importance  
744 because they shed a light on the less studied brain-gut axis in PD [135].

## 745 5. Conclusion

746 This review shows indisputable implications of several neuropeptides in the neuroprotection or  
747 symptoms in PD. Orexin alleviates the motor impairment, regulates the sleep disorders and  
748 improves hypothalamic memory in PD pathology. AII activates the pro-inflammatory pathways via  
749 its AT1 receptor and increases DA neuronal cell death, but protects the latter via activation of its  
750 AR2 receptor. VIP also activates its anti-apoptotic and anti-oxidative stress activity to insure the  
751 protection for the DA neurons. Carnosine was found to be able to alleviate motor symptoms by  
752 protecting against oxidative stress neural inflammation and mitochondrial dysfunction in PD.

753 Opioids disruption in the basal ganglia and striatum is highly linked with LID but it's unclear  
754 whether it's a compensatory mechanism or the cause of the symptom itself. Lastly PACAP seem to  
755 exhibit a neuroprotective of effect on striatal neurons in vivo and in vitro through regulation of  
756 apoptosis and inflammation. The presented findings urge the need for a shift towards a more  
757 advanced understanding of neuropeptides mechanism and involvement in clinical trials. Further  
758 studies need to take in consideration the major limitations found in the reviewed studies such as the  
759 sex difference between group subjects, the small sample size used in a study, and the lack of results  
760 verification through the use of multiple techniques. The difference in animal models used in studies  
761 sometimes yielded difference in the results even when same measurement techniques were applied  
762 making a deeper understanding of the molecular aspect of each animal model very important for a  
763 more unified assessment of Parkinson pathophysiology and symptoms. It's also important to take  
764 into consideration that the basal ganglia have many subdivisions and roles, that's why a more  
765 detailed and specific approach needs to be applied. This specific approach firstly, help to unravel a  
766 more zoomed in effect of these peptides on the basal ganglia's more specific regions to help in  
767 future development of a targeted therapeutic approach. And secondly, aid in the construction of a  
768 more global view to understand the multi-level effect of these peptides on brain tissues.

769

## 770 6. Conflict of interest

771 None.

## 772 7. Acknowledgements

773 None.

## 774 8. Abbreviations

775 CNS: central nervous system ; PD : Parkinson's disease; SN: substantia niagra; PACAP: pituitary adenylate cyclase  
776 activating polypeptide ; VIP: vasoactive intestinal peptide ; SNpc: substantia niagra pars compacta; MSNs: striatal  
777 medium spiny neurons; GABA: gamma-aminobutyric acid; STN: subthalamic nucleus; DA: dopamine; ROS: oxygen  
778 reactive species; iNOS: inducible nitric oxide synthase; NOS: nitric oxide synthase; MPTP: 1-methyl-4-phenyl-1,2,3,6-  
779 tetrahydropyridine; 6-OHDA: 6-hydroxydopamine; BBB: blood brain barrier; DAT: dopamine transporter; MFB:  
780 medial forebrain bundle; UPS: ubiquitin proteasome system; ALP: autophagy-lysosomal pathways; CSF: cerebrospinal  
781 fluid; NPY: neuropeptide Y; ODN: octadecaneuropeptide; VGF: nerve growth hormone; GIP: gastrointestinal peptide;

782 PP: pancreatic peptide; LH: lateral hypothalamus; LC: locus coeruleus; DR: dorsal raphe; Arc: arcuate nucleus; VMH:  
783 ventromedial hypothalamic nucleus; VTA: ventral tegmental area; GPCRs : protein-coupled receptors; OX1R: orexin  
784 receptor 1; OX2R: orexin receptor 2; MS: multiple sclerosis; UPDRS III: unified parkinson's disease rating scale part  
785 III; EDS: excessive day time sleep; REM: rapid eye movement; GP: globus pallidus; DREADD: designer receptors  
786 exclusively activated by designer drugs; GAD65: glutamic acid decarboxylase 65kD; cAMP: cyclic adenosine  
787 monophosphate; mPFC: medial prefrontal cortex; PPE or PPE-A: preproenkephalin; Pdyn or PPE-B: prodynorphin;  
788 MSH: melanocyte-stimulating hormone; ACTH: adrenocorticotrophic hormone; KOPR: kappa opioids receptor; MOPR:  
789 mu opioids receptors; DOPR: delta opioids receptors; LID: L-dopa induced dyskinesia; LTP: long-term potentiation;  
790 NMDA: N-methyl-D-aspartate; KO: kappa opioids; DADLE: D-Ala2, D-Leu5-enkephalin; OFQ/N: orpahn FQ or  
791 nocicpetin; IL: interleukin; GHRH: growth hormone releasing hormone; PAC1-R: PAC1-receptor; VPAC1-R: VPAC1-  
792 receptor; VPAC2-R: VPAC2-receptor; SOD: superoxide dismutase; CAT: catalase; CARP : cationic Arginine-rich  
793 peptide; L-dopa: levodopa; HVAC: Homovanillic acid; PAM: positive allosteric modulation; ERK: Extracellular  
794 signal-regulated kinases; VATH: ventral anterior nucleus of the thalamus; NGF: nerve growth factor; RMCPII : rat  
795 mast cell protease II; NuIP or Nurr1: nuclear receptor 1; RAS: renin-angiotensin-systems; ACE: angiotensin-converting  
796 enzyme; AII: angiotensin II; AT1R: angiotensin receptors type 1; AT2R: angiotensin receptors type 2; NADPH:  
797 nicotinamide adenine dinucleotide phosphate; NO: nitric oxid; MAPK: mitogen-activated protein kinase; PKC: protein  
798 kinase C; NOX4: NADPH oxidase 4 ; mito(KATP): mitochondrial ATP-sensitive potassium channel; GPX: glutathione  
799 peroxidase; SOD: superoxide dismutase; SAPK: stress-activated protein kinases; JNK: jun amino-terminal kinases;  
800 *Tnfa*: tumor necrosis factor-alpha; *Cox2*: cyclooxygenase 2; *Tlr4*: toll-like receptor 4; Trem1: triggering receptor  
801 expressed on myeloid cells; TNF- $\alpha$  : tumour necrosis factor alpha; PKA: protein kinase A; CREB: cAMP response  
802 element binding protein; BDNF: brain-derived neurotrophic factor; PG-j2: prostaglandin j2; PARK7 : protein coding  
803 gene associated with PD7; PSF: proapoptotic protein-associated splicing factor; PP: pancreatic polypeptide;  
804 AKT: protein kinase B; PSD-95: postsynaptic density protein 95; mGluR1: metabotropic glutamate receptor;  
805 ODN: octadecaneuropeptide; PPN: pedunculopontine nucleus.

806

## 807 **References**

- 808 [1] S. D. Kim, N. E. Allen, C. G. Canning, and V. S. C. Fung, "Parkinson disease," in *Handbook of*  
809 *Clinical Neurology*, vol. 159, Elsevier, 2018, pp. 173–193. doi: 10.1016/B978-0-444-63916-5.00011-2.
- 810 [2] A. Berardelli, J. C. Rothwell, P. D. Thompson, and M. Hallett, "Pathophysiology of bradykinesia in  
811 Parkinson's disease," *Brain J. Neurol.*, vol. 124, no. Pt 11, pp. 2131–2146, Nov. 2001, doi:  
812 10.1093/brain/124.11.2131.
- 813 [3] L. V. Kalia and A. E. Lang, "Parkinson's disease," *The Lancet*, vol. 386, no. 9996, pp. 896–912,  
814 Aug. 2015, doi: 10.1016/S0140-6736(14)61393-3.



- 815 [4] K. M. Prakash, N. V. Nadkarni, W.-K. Lye, M.-H. Yong, and E.-K. Tan, “The impact of non-motor  
816 symptoms on the quality of life of Parkinson’s disease patients: a longitudinal study,” *Eur. J. Neurol.*, vol.  
817 23, no. 5, pp. 854–860, May 2016, doi: 10.1111/ene.12950.
- 818 [5] S. Jain and D. S. Goldstein, “What ARE Parkinson disease? Non-motor features transform  
819 conception of the shaking palsy,” *Neurobiol. Dis.*, vol. 46, no. 3, pp. 505–507, Jun. 2012, doi:  
820 10.1016/j.nbd.2012.04.013.
- 821 [6] W. Muangpaisan, A. Mathews, H. Hori, and D. Seidel, “A systematic review of the worldwide  
822 prevalence and incidence of Parkinson’s disease,” *J. Med. Assoc. Thai. Chotmai het Thangphaet*, vol. 94, no.  
823 6, pp. 749–755, Jun. 2011.
- 824 [7] P. Calabresi, B. Picconi, A. Tozzi, V. Ghiglieri, and M. Di Filippo, “Direct and indirect pathways of  
825 basal ganglia: a critical reappraisal,” *Nat. Neurosci.*, vol. 17, no. 8, pp. 1022–1030, Aug. 2014, doi:  
826 10.1038/nn.3743.
- 827 [8] M. Skrzypski, M. Billert, K. W. Nowak, and M. Z. Strowski, “The role of orexin in controlling the  
828 activity of the adipo-pancreatic axis,” *J. Endocrinol.*, vol. 238, no. 2, pp. R95–R108, Aug. 2018, doi:  
829 10.1530/JOE-18-0122.
- 830 [9] L. Stefanis, “ $\alpha$ -Synuclein in Parkinson’s Disease,” *Cold Spring Harb. Perspect. Med.*, vol. 2, no. 2,  
831 p. a009399, Feb. 2012, doi: 10.1101/cshperspect.a009399.
- 832 [10] E. Maries, B. Dass, T. J. Collier, J. H. Kordower, and K. Steece-Collier, “The role of  $\alpha$ -synuclein in  
833 Parkinson’s disease: insights from animal models,” *Nat. Rev. Neurosci.*, vol. 4, no. 9, pp. 727–738, Sep.  
834 2003, doi: 10.1038/nrn1199.
- 835 [11] L. Xu and J. Pu, “Alpha-Synuclein in Parkinson’s Disease: From Pathogenetic Dysfunction to  
836 Potential Clinical Application,” *Park. Dis.*, vol. 2016, p. e1720621, Aug. 2016, doi: 10.1155/2016/1720621.
- 837 [12] W. Poewe *et al.*, “Parkinson disease,” *Nat. Rev. Dis. Primer*, vol. 3, p. 17013, Mar. 2017, doi:  
838 10.1038/nrdp.2017.13.
- 839 [13] L. Puspita, S. Y. Chung, and J.-W. Shim, “Oxidative stress and cellular pathologies in Parkinson’s  
840 disease,” *Mol. Brain*, vol. 10, no. 1, p. 53, Nov. 2017, doi: 10.1186/s13041-017-0340-9.
- 841 [14] “Oxidative Stress: Harms and Benefits for Human Health.”  
842 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5551541/> (accessed Aug. 27, 2021).
- 843 [15] S. J.-P. Haas, X. Zhou, V. Machado, A. Wree, K. Krieglstein, and B. Spittau, “Expression of Tgfb $\beta$ 1  
844 and Inflammatory Markers in the 6-hydroxydopamine Mouse Model of Parkinson’s Disease,” *Front. Mol.*  
845 *Neurosci.*, vol. 9, p. 7, Feb. 2016, doi: 10.3389/fnmol.2016.00007.
- 846 [16] J. R. Pereira *et al.*, “IL-6 serum levels are elevated in Parkinson’s disease patients with fatigue  
847 compared to patients without fatigue,” *J. Neurol. Sci.*, vol. 370, pp. 153–156, Nov. 2016, doi:  
848 10.1016/j.jns.2016.09.030.
- 849 [17] Q. Wang, Y. Liu, and J. Zhou, “Neuroinflammation in Parkinson’s disease and its potential as  
850 therapeutic target,” *Transl. Neurodegener.*, vol. 4, no. 1, p. 19, Dec. 2015, doi: 10.1186/s40035-015-0042-0.
- 851 [18] B. J. Ryan, S. Hoek, E. A. Fon, and R. Wade-Martins, “Mitochondrial dysfunction and mitophagy in  
852 Parkinson’s: from familial to sporadic disease,” *Trends Biochem. Sci.*, vol. 40, no. 4, pp. 200–210, Apr.  
853 2015, doi: 10.1016/j.tibs.2015.02.003.

- 854 [19] M. Rango, G. Dossi, L. Squarcina, and C. Bonifati, "Brain mitochondrial impairment in early-onset  
855 Parkinson's disease with or without PINK1 mutation," *Mov. Disord. Off. J. Mov. Disord. Soc.*, vol. 35, no. 3,  
856 pp. 504–507, Mar. 2020, doi: 10.1002/mds.27946.
- 857 [20] A. Bose and M. F. Beal, "Mitochondrial dysfunction in Parkinson's disease," *J. Neurochem.*, vol.  
858 139 Suppl 1, pp. 216–231, Oct. 2016, doi: 10.1111/jnc.13731.
- 859 [21] F. Blandini and M.-T. Armentero, "Animal models of Parkinson's disease," *FEBS J.*, vol. 279, no. 7,  
860 pp. 1156–1166, Apr. 2012, doi: 10.1111/j.1742-4658.2012.08491.x.
- 861 [22] V. Licker and P. R. Burkhard, "Proteomics as a new paradigm to tackle Parkinson's disease research  
862 challenges," *Transl. Proteomics*, vol. 4–5, pp. 1–17, Dec. 2014, doi: 10.1016/j.trprot.2014.08.001.
- 863 [23] C. J. Werner, R. Heyny-von Haussen, G. Mall, and S. Wolf, "Proteome analysis of human substantia  
864 nigra in Parkinson's disease," *Proteome Sci.*, vol. 6, p. 8, Feb. 2008, doi: 10.1186/1477-5956-6-8.
- 865 [24] Y. Zheng, L. Zhang, J. Xie, and L. Shi, "The Emerging Role of Neuropeptides in Parkinson's  
866 Disease," *Front. Aging Neurosci.*, vol. 13, 2021, doi: 10.3389/fnagi.2021.646726.
- 867 [25] J. Forbes and K. Krishnamurthy, "Biochemistry, Peptide," in *StatPearls*, Treasure Island (FL):  
868 StatPearls Publishing, 2021. Accessed: Aug. 25, 2021. [Online]. Available:  
869 <http://www.ncbi.nlm.nih.gov/books/NBK562260/>
- 870 [26] B. Jp, "What are neuropeptides?," *Methods Mol. Biol. Clifton NJ*, vol. 789, 2011, doi: 10.1007/978-  
871 1-61779-310-3\_1.
- 872 [27] A. F. Russo, "Overview of Neuropeptides: Awakening the Senses?," *Headache*, vol. 57 Suppl 2, pp.  
873 37–46, May 2017, doi: 10.1111/head.13084.
- 874 [28] T. Sakurai *et al.*, "Orexins and orexin receptors: a family of hypothalamic neuropeptides and G  
875 protein-coupled receptors that regulate feeding behavior," *Cell*, vol. 92, no. 4, pp. 573–585, Feb. 1998, doi:  
876 10.1016/s0092-8674(00)80949-6.
- 877 [29] L. de Lecea *et al.*, "The hypocretins: Hypothalamus-specific peptides with neuroexcitatory activity,"  
878 *Proc. Natl. Acad. Sci. U. S. A.*, vol. 95, no. 1, pp. 322–327, Jan. 1998.
- 879 [30] A. L. Gotter, A. L. Webber, P. J. Coleman, J. J. Renger, and C. J. Winrow, "International Union of  
880 Basic and Clinical Pharmacology. LXXXVI. Orexin receptor function, nomenclature and pharmacology,"  
881 *Pharmacol. Rev.*, vol. 64, no. 3, pp. 389–420, Jul. 2012, doi: 10.1124/pr.111.005546.
- 882 [31] T. E. Scammell, "Wakefulness: An eye-opening perspective on orexin neurons," *Curr. Biol.*, vol. 11,  
883 no. 19, pp. R769–R771, Oct. 2001, doi: 10.1016/S0960-9822(01)00466-3.
- 884 [32] T. Voisin, P. Rouet-Benzineb, N. Reuter, and M. Laburthe, "Orexins and their receptors: structural  
885 aspects and role in peripheral tissues," *Cell. Mol. Life Sci. CMLS*, vol. 60, no. 1, pp. 72–87, Jan. 2003, doi:  
886 10.1007/s000180300005.
- 887 [33] C. Wang *et al.*, "The Orexin/Receptor System: Molecular Mechanism and Therapeutic Potential for  
888 Neurological Diseases," *Front. Mol. Neurosci.*, vol. 11, p. 220, Jun. 2018, doi: 10.3389/fnmol.2018.00220.
- 889 [34] J. M. Siegel, R. Moore, T. Thannickal, and R. Nienhuis, "A brief history of hypocretin/orexin and  
890 narcolepsy," *Neuropsychopharmacol. Off. Publ. Am. Coll. Neuropsychopharmacol.*, vol. 25, no. 5 Suppl, pp.  
891 S14–20, Nov. 2001, doi: 10.1016/S0893-133X(01)00317-7.

- 892 [35] R. Fronczek, C. R. Baumann, G. J. Lammers, C. L. Bassetti, and S. Overeem, "Hypocretin/orexin  
893 disturbances in neurological disorders," *Sleep Med. Rev.*, vol. 13, no. 1, pp. 9–22, Feb. 2009, doi:  
894 10.1016/j.smrv.2008.05.002.
- 895 [36] S. Huang *et al.*, "Increased plasma orexin-A concentrations are associated with the non-motor  
896 symptoms in Parkinson's disease patients," *Neurosci. Lett.*, vol. 741, p. 135480, Jan. 2021, doi:  
897 10.1016/j.neulet.2020.135480.
- 898 [37] X. Drouot *et al.*, "Low level of ventricular CSF orexin-A is not associated with objective sleepiness  
899 in PD," *Sleep Med.*, vol. 12, no. 9, pp. 936–937, Oct. 2011, doi: 10.1016/j.sleep.2011.08.002.
- 900 [38] R. Fronczek *et al.*, "Hypocretin (orexin) loss in Parkinson's disease," *Brain J. Neurol.*, vol. 130, no.  
901 Pt 6, pp. 1577–1585, Jun. 2007, doi: 10.1093/brain/awm090.
- 902 [39] Y. Compta *et al.*, "Cerebrospinal hypocretin, daytime sleepiness and sleep architecture in  
903 Parkinson's disease dementia," *Brain J. Neurol.*, vol. 132, no. Pt 12, pp. 3308–3317, Dec. 2009, doi:  
904 10.1093/brain/awp263.
- 905 [40] D. Gerashchenko *et al.*, "Relationship between CSF hypocretin levels and hypocretin neuronal loss,"  
906 *Exp. Neurol.*, vol. 184, no. 2, pp. 1010–1016, Dec. 2003, doi: 10.1016/S0014-4886(03)00388-1.
- 907 [41] M. Wienecke *et al.*, "Progressive dopamine and hypocretin deficiencies in Parkinson's disease: is  
908 there an impact on sleep and wakefulness?," *J. Sleep Res.*, vol. 21, no. 6, pp. 710–717, Dec. 2012, doi:  
909 10.1111/j.1365-2869.2012.01027.x.
- 910 [42] H. Asai *et al.*, "Cerebrospinal fluid-orexin levels and sleep attacks in four patients with Parkinson's  
911 disease," *Clin. Neurol. Neurosurg.*, vol. 111, no. 4, pp. 341–344, May 2009, doi:  
912 10.1016/j.clineuro.2008.11.007.
- 913 [43] A. Bridoux *et al.*, "Ventricular orexin-A (hypocretin-1) levels correlate with rapid-eye-movement  
914 sleep without atonia in Parkinson's disease," *Nat. Sci. Sleep*, vol. 5, pp. 87–91, 2013, doi:  
915 10.2147/NSS.S41245.
- 916 [44] Z. Hadadianpour, F. Fatehi, F. Ayoobi, A. Kaeidi, A. Shamsizadeh, and I. Fatemi, "The effect of  
917 orexin-A on motor and cognitive functions in a rat model of Parkinson's disease," *Neurol. Res.*, vol. 39, no.  
918 9, pp. 845–851, Sep. 2017, doi: 10.1080/01616412.2017.1352185.
- 919 [45] Y. Xue *et al.*, "Orexin-A increases the activity of globus pallidus neurons in both normal and  
920 parkinsonian rats," *Eur. J. Neurosci.*, vol. 44, no. 5, pp. 2247–2257, Sep. 2016, doi: 10.1111/ejn.13323.
- 921 [46] Y. Wang *et al.*, "Orexins alleviate motor deficits via increasing firing activity of pallidal neurons in a  
922 mouse model of Parkinson's disease," *Am. J. Physiol. Cell Physiol.*, vol. 317, no. 4, pp. C800–C812, Oct.  
923 2019, doi: 10.1152/ajpcell.00125.2019.
- 924 [47] W. Poewe *et al.*, "Parkinson disease," *Nat. Rev. Dis. Primer*, vol. 3, p. 17013, Mar. 2017, doi:  
925 10.1038/nrdp.2017.13.
- 926 [48] H.-R. Gao *et al.*, "Orexin Directly Enhances the Excitability of Globus Pallidus Internus Neurons in  
927 Rat by Co-activating OX1 and OX2 Receptors," *Neurosci. Bull.*, vol. 33, no. 4, pp. 365–372, Apr. 2017, doi:  
928 10.1007/s12264-017-0127-0.
- 929 [49] Q. Sheng *et al.*, "The Subthalamic Neurons are Activated by Both Orexin-A and Orexin-B,"  
930 *Neuroscience*, vol. 369, pp. 97–108, Jan. 2018, doi: 10.1016/j.neuroscience.2017.11.008.

- 931 [50] X.-Y. Zhang, L. Yu, Q.-X. Zhuang, J.-N. Zhu, and J.-J. Wang, "Central functions of the orexinergic  
932 system," *Neurosci. Bull.*, vol. 29, no. 3, pp. 355–365, Jun. 2013, doi: 10.1007/s12264-012-1297-4.
- 933 [51] M. Stanojlovic, J. P. Pallais, and C. M. Kotz, "Inhibition of Orexin/Hypocretin Neurons Ameliorates  
934 Elevated Physical Activity and Energy Expenditure in the A53T Mouse Model of Parkinson's Disease," *Int.*  
935 *J. Mol. Sci.*, vol. 22, no. 2, p. 795, Jan. 2021, doi: 10.3390/ijms22020795.
- 936 [52] M. Stanojlovic, J. P. Pallais, and C. M. Kotz, "Chemogenetic Modulation of Orexin Neurons  
937 Reverses Changes in Anxiety and Locomotor Activity in the A53T Mouse Model of Parkinson's Disease,"  
938 *Front. Neurosci.*, vol. 13, p. 702, 2019, doi: 10.3389/fnins.2019.00702.
- 939 [53] C. Kosse, C. Schöne, E. Bracey, and D. Burdakov, "Orexin-driven GAD65 network of the lateral  
940 hypothalamus sets physical activity in mice," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 114, no. 17, pp. 4525–  
941 4530, Apr. 2017, doi: 10.1073/pnas.1619700114.
- 942 [54] M. Stanojlovic, J. P. Pallais, M. K. Lee, and C. M. Kotz, "Pharmacological and chemogenetic  
943 orexin/hypocretin intervention ameliorates Hipp-dependent memory impairment in the A53T mice model of  
944 Parkinson's disease," *Mol. Brain*, vol. 12, no. 1, p. 87, Oct. 2019, doi: 10.1186/s13041-019-0514-8.
- 945 [55] S. M, P. Y. Jp, V. A, and K. C, "Early Sociability and Social Memory Impairment in the A53T  
946 Mouse Model of Parkinson's Disease Are Ameliorated by Chemogenetic Modulation of Orexin Neuron  
947 Activity," *Mol. Neurobiol.*, vol. 56, no. 12, Dec. 2019, doi: 10.1007/s12035-019-01682-x.
- 948 [56] L. Yang *et al.*, "Hypocretin/orexin neurons contribute to hippocampus-dependent social memory and  
949 synaptic plasticity in mice," *J. Neurosci. Off. J. Soc. Neurosci.*, vol. 33, no. 12, pp. 5275–5284, Mar. 2013,  
950 doi: 10.1523/JNEUROSCI.3200-12.2013.
- 951 [57] I. S. Zagon and P. J. McLaughlin, "Endogenous Opioids in the Etiology and Treatment of Multiple  
952 Sclerosis," in *Multiple Sclerosis: Perspectives in Treatment and Pathogenesis*, I. S. Zagon and P. J.  
953 McLaughlin, Eds. Brisbane (AU): Codon Publications, 2017. Accessed: Aug. 26, 2021. [Online]. Available:  
954 <http://www.ncbi.nlm.nih.gov/books/NBK470156/>
- 955 [58] E. E. Benarroch, "Endogenous opioid systems: Current concepts and clinical correlations,"  
956 *Neurology*, vol. 79, no. 8, pp. 807–814, Aug. 2012, doi: 10.1212/WNL.0b013e3182662098.
- 957 [59] A. Ljungdahl, J. Hanrieder, M. Fälth, J. Bergquist, and M. Andersson, "Imaging Mass Spectrometry  
958 Reveals Elevated Nigral Levels of Dynorphin Neuropeptides in L-DOPA-Induced Dyskinesia in Rat Model  
959 of Parkinson's Disease," *PLoS ONE*, vol. 6, no. 9, p. e25653, Sep. 2011, doi: 10.1371/journal.pone.0025653.
- 960 [60] R. Al-Hasani and M. R. Bruchas, "Molecular Mechanisms of Opioid Receptor-Dependent Signaling  
961 and Behavior," *Anesthesiology*, vol. 115, no. 6, pp. 1363–1381, Dec. 2011, doi:  
962 10.1097/ALN.0b013e318238bba6.
- 963 [61] R. J. Bodnar, "Endogenous opiates and behavior: 2019," *Peptides*, vol. 141, p. 170547, Jul. 2021,  
964 doi: 10.1016/j.peptides.2021.170547.
- 965 [62] H. Steiner and C. R. Gerfen, "Role of dynorphin and enkephalin in the regulation of striatal output  
966 pathways and behavior," *Exp. Brain Res.*, vol. 123, no. 1–2, pp. 60–76, Nov. 1998, doi:  
967 10.1007/s002210050545.

- 968 [63] X.-Y. Chen, Y. Xue, H. Chen, and L. Chen, "The globus pallidus as a target for neuropeptides and  
969 endocannabinoids participating in central activities," *Peptides*, vol. 124, p. 170210, Feb. 2020, doi:  
970 10.1016/j.peptides.2019.170210.
- 971 [64] J. Pan and H. Cai, "Opioid system in L-DOPA-induced dyskinesia," *Transl. Neurodegener.*, vol. 6,  
972 p. 1, 2017, doi: 10.1186/s40035-017-0071-y.
- 973 [65] J. Hanrieder, A. Ljungdahl, M. Fälth, S. E. Mammo, J. Bergquist, and M. Andersson, "L-DOPA-  
974 induced dyskinesia is associated with regional increase of striatal dynorphin peptides as elucidated by  
975 imaging mass spectrometry," *Mol. Cell. Proteomics MCP*, vol. 10, no. 10, p. M111.009308, Oct. 2011, doi:  
976 10.1074/mcp.M111.009308.
- 977 [66] L. F. Potts *et al.*, "Dual  $\kappa$ -agonist /  $\mu$ -antagonist opioid receptor modulation reduces L-dopa induced  
978 dyskinesia and corrects dysregulated striatal changes in the non-human primate model of Parkinson's  
979 disease," *Ann. Neurol.*, vol. 77, no. 6, pp. 930–941, Jun. 2015, doi: 10.1002/ana.24375.
- 980 [67] A. Vinuela *et al.*, "Implanted reuptake-deficient or wild-type dopaminergic neurons improve ON 1-  
981 dopa dyskinesias without OFF-d dyskinesias in a rat model of Parkinson's disease," *Brain*, vol. 131, no. 12,  
982 pp. 3361–3379, Dec. 2008, doi: 10.1093/brain/awn192.
- 983 [68] L. Frau, M. Morelli, and N. Simola, "Performance of movement in hemiparkinsonian rats influences  
984 the modifications induced by dopamine agonists in striatal efferent dynorphinergic neurons," *Exp. Neurol.*,  
985 vol. 247, pp. 663–672, Sep. 2013, doi: 10.1016/j.expneurol.2013.03.002.
- 986 [69] A. Nilsson *et al.*, "Striatal Alterations of Secretogranin-1, Somatostatin, Prodynorphin, and  
987 Cholecystokinin Peptides in an Experimental Mouse Model of Parkinson Disease," *Mol. Cell. Proteomics*  
988 *MCP*, vol. 8, no. 5, pp. 1094–1104, May 2009, doi: 10.1074/mcp.M800454-MCP200.
- 989 [70] L. Jouve, P. Salin, C. Melon, and L. Kerkerian-Le Goff, "Deep brain stimulation of the center  
990 median-parafascicular complex of the thalamus has efficient anti-parkinsonian action associated with  
991 widespread cellular responses in the basal ganglia network in a rat model of Parkinson's disease," *J.*  
992 *Neurosci. Off. J. Soc. Neurosci.*, vol. 30, no. 29, pp. 9919–9928, Jul. 2010, doi: 10.1523/JNEUROSCI.1404-  
993 10.2010.
- 994 [71] Y. Y. Yien and B. H. Paw, "A role for iron deficiency in dopaminergic neurodegeneration," *Proc.*  
995 *Natl. Acad. Sci. U. S. A.*, vol. 113, no. 13, p. 3417, Mar. 2016, doi: 10.1073/pnas.1601976113.
- 996 [72] Y.-M. J. Sun, T. Hoang, J. A. Neubauer, and A. S. Walters, "Opioids protect against substantia nigra  
997 cell degeneration under conditions of iron deprivation: a mechanism of possible relevance to the Restless  
998 Legs Syndrome (RLS) and Parkinson's disease," *J. Neurol. Sci.*, vol. 304, no. 1–2, pp. 93–101, May 2011,  
999 doi: 10.1016/j.jns.2011.02.003.
- 1000 [73] A. J. Harmar *et al.*, "Pharmacology and functions of receptors for vasoactive intestinal peptide and  
1001 pituitary adenylate cyclase-activating polypeptide: IUPHAR Review 1," *Br. J. Pharmacol.*, vol. 166, no. 1,  
1002 pp. 4–17, May 2012, doi: 10.1111/j.1476-5381.2012.01871.x.
- 1003 [74] S. I. Said and V. Mutt, "Polypeptide with broad biological activity: isolation from small intestine,"  
1004 *Science*, vol. 169, no. 3951, pp. 1217–1218, Sep. 1970, doi: 10.1126/science.169.3951.1217.
- 1005 [75] M. Iwasaki, Y. Akiba, and J. D. Kaunitz, "Recent advances in vasoactive intestinal peptide  
1006 physiology and pathophysiology: focus on the gastrointestinal system," *F1000Research*, vol. 8, p. F1000  
1007 Faculty Rev-1629, Sep. 2019, doi: 10.12688/f1000research.18039.1.

- 1008 [76] F. Giancola *et al.*, “Downregulation of neuronal vasoactive intestinal polypeptide in Parkinson’s  
1009 disease and chronic constipation,” *Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc.*, vol. 29,  
1010 no. 5, May 2017, doi: 10.1111/nmo.12995.
- 1011 [77] T. Hirabayashi, T. Nakamachi, and S. Shioda, “Discovery of PACAP and its receptors in the brain,”  
1012 *J. Headache Pain*, vol. 19, no. 1, p. 28, Apr. 2018, doi: 10.1186/s10194-018-0855-1.
- 1013 [78] N. Tunçel, O. T. Korkmaz, N. Tekin, E. Şener, F. Akyüz, and M. Inal, “Antioxidant and anti-  
1014 apoptotic activity of vasoactive intestinal peptide (VIP) against 6-hydroxy dopamine toxicity in the rat  
1015 corpus striatum,” *J. Mol. Neurosci. MN*, vol. 46, no. 1, pp. 51–57, Jan. 2012, doi: 10.1007/s12031-011-9618-  
1016 z.
- 1017 [79] R. Yu *et al.*, “TAT-tagging of VIP exerts positive allosteric modulation of the PAC1 receptor and  
1018 enhances VIP neuroprotective effect in the MPTP mouse model of Parkinson’s disease,” *Biochim. Biophys.*  
1019 *Acta Gen. Subj.*, vol. 1864, no. 8, p. 129626, Aug. 2020, doi: 10.1016/j.bbagen.2020.129626.
- 1020 [80] O. Korkmaz, H. Ay, E. Ulupinar, and N. Tunçel, “Vasoactive intestinal peptide enhances striatal  
1021 plasticity and prevents dopaminergic cell loss in Parkinsonian rats,” *J. Mol. Neurosci. MN*, vol. 48, no. 3, pp.  
1022 565–573, Nov. 2012, doi: 10.1007/s12031-012-9781-x.
- 1023 [81] C. M. White, S. Ji, H. Cai, S. Maudsley, and B. Martin, “Therapeutic potential of vasoactive  
1024 intestinal peptide and its receptors in neurological disorders,” *CNS Neurol. Disord. Drug Targets*, vol. 9, no.  
1025 5, pp. 661–666, Nov. 2010.
- 1026 [82] K. E. Olson *et al.*, “Selective VIP Receptor Agonists Facilitate Immune Transformation for  
1027 Dopaminergic Neuroprotection in MPTP-Intoxicated Mice,” *J. Neurosci.*, vol. 35, no. 50, pp. 16463–16478,  
1028 Dec. 2015, doi: 10.1523/JNEUROSCI.2131-15.2015.
- 1029 [83] A. Bohush, G. Niewiadomska, and A. Filipek, “Role of Mitogen Activated Protein Kinase Signaling  
1030 in Parkinson’s Disease,” *Int. J. Mol. Sci.*, vol. 19, no. 10, p. 2973, Sep. 2018, doi: 10.3390/ijms19102973.
- 1031 [84] R. L. Mosley *et al.*, “A Synthetic Agonist to Vasoactive Intestinal Peptide Receptor-2 Induces  
1032 Regulatory T Cell Neuroprotective Activities in Models of Parkinson’s Disease,” *Front. Cell. Neurosci.*, vol.  
1033 13, p. 421, 2019, doi: 10.3389/fncel.2019.00421.
- 1034 [85] O. T. Korkmaz, N. Tunçel, M. Tunçel, E. M. Oncü, V. Sahintürk, and M. Celik, “Vasoactive  
1035 intestinal peptide (VIP) treatment of Parkinsonian rats increases thalamic gamma-aminobutyric acid (GABA)  
1036 levels and alters the release of nerve growth factor (NGF) by mast cells,” *J. Mol. Neurosci. MN*, vol. 41, no.  
1037 2, pp. 278–287, Jun. 2010, doi: 10.1007/s12031-009-9307-3.
- 1038 [86] İ. H. Yelkenli *et al.*, “Modulation of Corpus Striatum Neurochemistry by Astrocytes and Vasoactive  
1039 Intestinal Peptide (VIP) in Parkinsonian Rats,” *J. Mol. Neurosci. MN*, vol. 59, no. 2, pp. 280–289, Jun. 2016,  
1040 doi: 10.1007/s12031-016-0757-0.
- 1041 [87] H. J. Federoff, “Nur(R1) turing a notion on the etiopathogenesis of Parkinson’s disease,” *Neurotox.*  
1042 *Res.*, vol. 16, no. 3, pp. 261–270, Oct. 2009, doi: 10.1007/s12640-009-9056-7.
- 1043 [88] C. Jia *et al.*, “ $\alpha$ -Synuclein Negatively Regulates Nurr1 Expression Through NF- $\kappa$ B-Related  
1044 Mechanism,” *Front. Mol. Neurosci.*, vol. 0, 2020, doi: 10.3389/fnmol.2020.00064.

- 1045 [89] A. Mascolo *et al.*, “New and old roles of the peripheral and brain renin-angiotensin-aldosterone  
1046 system (RAAS): Focus on cardiovascular and neurological diseases,” *Int. J. Cardiol.*, vol. 227, pp. 734–742,  
1047 Jan. 2017, doi: 10.1016/j.ijcard.2016.10.069.
- 1048 [90] E. Farag *et al.*, “The renin angiotensin system and the brain: New developments,” *J. Clin. Neurosci.*  
1049 *Off. J. Neurosurg. Soc. Australas.*, vol. 46, pp. 1–8, Dec. 2017, doi: 10.1016/j.jocn.2017.08.055.
- 1050 [91] M. J. McKinley *et al.*, “The brain renin-angiotensin system: location and physiological roles,” *Int. J.*  
1051 *Biochem. Cell Biol.*, vol. 35, no. 6, pp. 901–918, Jun. 2003, doi: 10.1016/s1357-2725(02)00306-0.
- 1052 [92] W. M. Zawada *et al.*, “Loss of angiotensin II receptor expression in dopamine neurons in  
1053 Parkinson’s disease correlates with pathological progression and is accompanied by increases in Nox4- and  
1054 8-OH guanosine-related nucleic acid oxidation and caspase-3 activation,” *Acta Neuropathol. Commun.*, vol.  
1055 3, p. 9, Feb. 2015, doi: 10.1186/s40478-015-0189-z.
- 1056 [93] C. Cosarderelioglu *et al.*, “Brain Renin–Angiotensin System at the Intersect of Physical and  
1057 Cognitive Frailty,” *Front. Neurosci.*, vol. 14, p. 981, 2020, doi: 10.3389/fnins.2020.586314.
- 1058 [94] N. P. Rocha *et al.*, “Peripheral levels of angiotensins are associated with depressive symptoms in  
1059 Parkinson’s disease,” *J. Neurol. Sci.*, vol. 368, pp. 235–239, Sep. 2016, doi: 10.1016/j.jns.2016.07.031.
- 1060 [95] Q. Gao *et al.*, “Azilsartan ameliorates apoptosis of dopaminergic neurons and rescues characteristic  
1061 parkinsonian behaviors in a rat model of Parkinson’s disease,” *Oncotarget*, vol. 8, no. 15, pp. 24099–24109,  
1062 Apr. 2017, doi: 10.18632/oncotarget.15732.
- 1063 [96] A. I. Rodriguez-Perez, R. Valenzuela, B. Villar-Cheda, M. J. Guerra, J. L. Lanciego, and J. L.  
1064 Labandeira-Garcia, “Estrogen and angiotensin interaction in the substantia nigra. Relevance to  
1065 postmenopausal Parkinson’s disease,” *Exp. Neurol.*, vol. 224, no. 2, pp. 517–526, Aug. 2010, doi:  
1066 10.1016/j.expneurol.2010.05.015.
- 1067 [97] J. Rodriguez-Pallares, J. A. Parga, B. Joglar, M. J. Guerra, and J. L. Labandeira-Garcia,  
1068 “Mitochondrial ATP-sensitive potassium channels enhance angiotensin-induced oxidative damage and  
1069 dopaminergic neuron degeneration. Relevance for aging-associated susceptibility to Parkinson’s disease,”  
1070 *Age*, vol. 34, no. 4, pp. 863–880, Aug. 2012, doi: 10.1007/s11357-011-9284-7.
- 1071 [98] B. Villar-Cheda *et al.*, “Nigral and striatal regulation of angiotensin receptor expression by  
1072 dopamine and angiotensin in rodents: implications for progression of Parkinson’s disease,” *Eur. J. Neurosci.*,  
1073 vol. 32, no. 10, pp. 1695–1706, Nov. 2010, doi: 10.1111/j.1460-9568.2010.07448.x.
- 1074 [99] B. Villar-Cheda, R. Valenzuela, A. I. Rodriguez-Perez, M. J. Guerra, and J. L. Labandeira-Garcia,  
1075 “Aging-related changes in the nigral angiotensin system enhances proinflammatory and pro-oxidative  
1076 markers and 6-OHDA-induced dopaminergic degeneration,” *Neurobiol. Aging*, vol. 33, no. 1, p. 204.e1–11,  
1077 Jan. 2012, doi: 10.1016/j.neurobiolaging.2010.08.006.
- 1078 [100] J. L. Labandeira-Garcia, A. I. Rodríguez-Perez, P. Garrido-Gil, J. Rodriguez-Pallares, J. L.  
1079 Lanciego, and M. J. Guerra, “Brain Renin-Angiotensin System and Microglial Polarization: Implications for  
1080 Aging and Neurodegeneration,” *Front. Aging Neurosci.*, vol. 9, p. 129, 2017, doi: 10.3389/fnagi.2017.00129.
- 1081 [101] A. A. Boldyrev, G. Aldini, and W. Derave, “Physiology and pathophysiology of carnosine,” *Physiol.*  
1082 *Rev.*, vol. 93, no. 4, pp. 1803–1845, Oct. 2013, doi: 10.1152/physrev.00039.2012.

- 1083 [102] M. Kawahara, K.-I. Tanaka, and M. Kato-Negishi, “Zinc, Carnosine, and Neurodegenerative  
1084 Diseases,” *Nutrients*, vol. 10, no. 2, p. E147, Jan. 2018, doi: 10.3390/nu10020147.
- 1085 [103] M. Schön *et al.*, “The Potential of Carnosine in Brain-Related Disorders: A Comprehensive Review  
1086 of Current Evidence,” *Nutrients*, vol. 11, no. 6, p. 1196, May 2019, doi: 10.3390/nu11061196.
- 1087 [104] A. Boldyrev *et al.*, “Carnosine [corrected] increases efficiency of DOPA therapy of Parkinson’s  
1088 disease: a pilot study,” *Rejuvenation Res.*, vol. 11, no. 4, pp. 821–827, Aug. 2008, doi:  
1089 10.1089/rej.2008.0716.
- 1090 [105] P. Sozio *et al.*, “New L-dopa codrugs as potential antiparkinson agents,” *Arch. Pharm. (Weinheim)*,  
1091 vol. 341, no. 7, pp. 412–417, Jul. 2008, doi: 10.1002/ardp.200700228.
- 1092 [106] M.-L. Bermúdez, K. B. Seroogy, and M. B. Genter, “Evaluation of Carnosine Intervention in the  
1093 Thy1-aSyn Mouse Model of Parkinson’s Disease,” *Neuroscience*, vol. 411, pp. 270–278, Jul. 2019, doi:  
1094 10.1016/j.neuroscience.2019.05.026.
- 1095 [107] M. Kubota, N. Kobayashi, T. Sugizaki, M. Shimoda, M. Kawahara, and K.-I. Tanaka, “Carnosine  
1096 suppresses neuronal cell death and inflammation induced by 6-hydroxydopamine in an in vitro model of  
1097 Parkinson’s disease,” *PLoS One*, vol. 15, no. 10, p. e0240448, 2020, doi: 10.1371/journal.pone.0240448.
- 1098 [108] S.-J. Tsai, W.-W. Kuo, W.-H. Liu, and M.-C. Yin, “Antioxidative and anti-inflammatory protection  
1099 from carnosine in the striatum of MPTP-treated mice,” *J. Agric. Food Chem.*, vol. 58, no. 21, pp. 11510–  
1100 11516, Nov. 2010, doi: 10.1021/jf103258p.
- 1101 [109] M.-L. Bermúdez, M. R. Skelton, and M. B. Genter, “Intranasal carnosine attenuates transcriptomic  
1102 alterations and improves mitochondrial function in the Thy1-aSyn mouse model of Parkinson’s disease,”  
1103 *Mol. Genet. Metab.*, vol. 125, no. 3, pp. 305–313, Nov. 2018, doi: 10.1016/j.ymgme.2018.08.002.
- 1104 [110] S. Shioda, F. Takenoya, N. Wada, T. Hirabayashi, T. Seki, and T. Nakamachi, “Pleiotropic and  
1105 retinoprotective functions of PACAP,” *Anat. Sci. Int.*, vol. 91, no. 4, pp. 313–324, Sep. 2016, doi:  
1106 10.1007/s12565-016-0351-0.
- 1107 [111] T. Hirabayashi, T. Nakamachi, and S. Shioda, “Discovery of PACAP and its receptors in the brain,”  
1108 *J. Headache Pain*, vol. 19, no. 1, p. 28, Apr. 2018, doi: 10.1186/s10194-018-0855-1.
- 1109 [112] A. Arimura, “Perspectives on pituitary adenylate cyclase activating polypeptide (PACAP) in the  
1110 neuroendocrine, endocrine, and nervous systems,” *Jpn. J. Physiol.*, vol. 48, no. 5, pp. 301–331, Oct. 1998,  
1111 doi: 10.2170/jjphysiol.48.301.
- 1112 [113] N. M. Sherwood, S. L. Krueckl, and J. E. McRory, “The Origin and Function of the Pituitary  
1113 Adenylate Cyclase-Activating Polypeptide (PACAP)/Glucagon Superfamily\*,” *Endocr. Rev.*, vol. 21, no. 6,  
1114 pp. 619–670, Dec. 2000, doi: 10.1210/edrv.21.6.0414.
- 1115 [114] G. Maasz *et al.*, “Pituitary adenylate cyclase-activating polypeptide (PACAP) has a neuroprotective  
1116 function in dopamine-based neurodegeneration in rat and snail parkinsonian models,” *Dis. Model. Mech.*,  
1117 vol. 10, no. 2, pp. 127–139, Feb. 2017, doi: 10.1242/dmm.027185.
- 1118 [115] R. Yu *et al.*, “TAT-tagging of VIP exerts positive allosteric modulation of the PAC1 receptor and  
1119 enhances VIP neuroprotective effect in the MPTP mouse model of Parkinson’s disease,” *Biochim. Biophys.*  
1120 *Acta Gen. Subj.*, vol. 1864, no. 8, p. 129626, Aug. 2020, doi: 10.1016/j.bbagen.2020.129626.



- 1121 [116] K.-Y. Shivers, A. Nikolopoulou, S. I. Machlovi, S. Vallabhajosula, and M. E. Figueiredo-Pereira,  
1122 “PACAP27 prevents Parkinson-like neuronal loss and motor deficits but not microglia activation induced by  
1123 prostaglandin J2,” *Biochim. Biophys. Acta*, vol. 1842, no. 9, pp. 1707–1719, Sep. 2014, doi:  
1124 10.1016/j.bbadis.2014.06.020.
- 1125 [117] D. Brown, A. Tamas, D. Reglodi, and Y. Tizabi, “PACAP protects against inflammatory-mediated  
1126 toxicity in dopaminergic SH-SY5Y cells: implication for Parkinson’s disease,” *Neurotox. Res.*, vol. 26, no. 3,  
1127 pp. 230–239, Oct. 2014, doi: 10.1007/s12640-014-9468-x.
- 1128 [118] K. Wakabayashi, K. Tanji, F. Mori, and H. Takahashi, “The Lewy body in Parkinson’s disease:  
1129 molecules implicated in the formation and degradation of alpha-synuclein aggregates,” *Neuropathol. Off. J.*  
1130 *Jpn. Soc. Neuropathol.*, vol. 27, no. 5, pp. 494–506, Oct. 2007, doi: 10.1111/j.1440-1789.2007.00803.x.
- 1131 [119] K. Knudsen *et al.*, “Pancreatic Polypeptide in Parkinson’s Disease: A Potential Marker of  
1132 Parasympathetic Denervation,” *J. Park. Dis.*, vol. 7, no. 4, pp. 645–652, 2017, doi: 10.3233/JPD-171189.
- 1133 [120] T. J. O’Toole and S. Sharma, “Physiology, Somatostatin,” in *StatPearls*, Treasure Island (FL):  
1134 StatPearls Publishing, 2021. Accessed: Aug. 20, 2021. [Online]. Available:  
1135 <http://www.ncbi.nlm.nih.gov/books/NBK538327/>
- 1136 [121] J. Lonovics, P. Devitt, L. C. Watson, P. L. Rayford, and J. C. Thompson, “Pancreatic polypeptide. A  
1137 review,” *Arch. Surg. Chic. Ill 1960*, vol. 116, no. 10, pp. 1256–1264, Oct. 1981, doi:  
1138 10.1001/archsurg.1981.01380220010002.
- 1139 [122] S. M, K. T, W. H, K. T, and H. Y, “Serum somatostatin in early-stage Parkinson’s disease,” *Acta*  
1140 *Neurol. Scand.*, vol. 121, no. 4, Apr. 2010, doi: 10.1111/j.1600-0404.2009.01178.x.
- 1141 [123] F. Escamilla-Sevilla *et al.*, “Change of the melanocortin system caused by bilateral subthalamic  
1142 nucleus stimulation in Parkinson’s disease,” *Acta Neurol. Scand.*, vol. 124, no. 4, pp. 275–281, Oct. 2011,  
1143 doi: 10.1111/j.1600-0404.2010.01469.x.
- 1144 [124] “Neuroprotection by neuropeptide Y in cell and animal models of Parkinson’s disease - PubMed.”  
1145 <https://pubmed.ncbi.nlm.nih.gov/21816512/> (accessed Aug. 20, 2021).
- 1146 [125] S. Bahdoudi *et al.*, “Neuroprotective effects of the gliopeptide ODN in an in vivo model of  
1147 Parkinson’s disease,” *Cell. Mol. Life Sci. CMLS*, vol. 75, no. 11, pp. 2075–2091, Jun. 2018, doi:  
1148 10.1007/s00018-017-2727-2.
- 1149 [126] J. L. Elson, R. Kochaj, R. Reynolds, and I. S. Pienaar, “Temporal-Spatial Profiling of  
1150 Pedunculopontine Galanin-Cholinergic Neurons in the Lactacystin Rat Model of Parkinson’s Disease,”  
1151 *Neurotox. Res.*, vol. 34, no. 1, pp. 16–31, Jul. 2018, doi: 10.1007/s12640-017-9846-2.
- 1152 [127] I. T. French and K. A. Muthusamy, “A Review of the Pedunculopontine Nucleus in Parkinson’s  
1153 Disease,” *Front. Aging Neurosci.*, vol. 10, p. 99, 2018, doi: 10.3389/fnagi.2018.00099.
- 1154 [128] Y. Li, W. Liu, L. Li, and C. Hölscher, “D-Ala2-GIP-glu-PAL is neuroprotective in a chronic  
1155 Parkinson’s disease mouse model and increases BDNF expression while reducing neuroinflammation and  
1156 lipid peroxidation,” *Eur. J. Pharmacol.*, vol. 797, pp. 162–172, Feb. 2017, doi:  
1157 10.1016/j.ejphar.2016.11.050.

- 1158 [129] C. H. S. McIntosh, S. Widenmaier, and S.-J. Kim, “Glucose-dependent insulintropic polypeptide  
1159 (Gastric Inhibitory Polypeptide; GIP),” *Vitam. Horm.*, vol. 80, pp. 409–471, 2009, doi: 10.1016/S0083-  
1160 6729(08)00615-8.
- 1161 [130] Z. Q. Zhang and C. Hölscher, “GIP has neuroprotective effects in Alzheimer and Parkinson’s disease  
1162 models,” *Peptides*, vol. 125, p. 170184, Mar. 2020, doi: 10.1016/j.peptides.2019.170184.
- 1163 [131] C. Cocco *et al.*, “Distribution of VGF peptides in the human cortex and their selective changes in  
1164 Parkinson’s and Alzheimer’s diseases,” *J. Anat.*, vol. 217, no. 6, pp. 683–693, Dec. 2010, doi:  
1165 10.1111/j.1469-7580.2010.01309.x.
- 1166 [132] T. Umehara, H. Oka, A. Nakahara, H. Matsuno, and C. Toyoda, “High norepinephrinergic  
1167 orthostatic hypotension in early Parkinson’s disease,” *Parkinsonism Relat. Disord.*, vol. 55, pp. 97–102, Oct.  
1168 2018, doi: 10.1016/j.parkreldis.2018.05.025.
- 1169 [133] “Peptides semax and selank affect the behavior of rats with 6-OHDA induced PD-like parkinsonism  
1170 - PubMed.” <https://pubmed.ncbi.nlm.nih.gov/28702721/> (accessed Aug. 21, 2021).
- 1171 [134] A. Niewiarowska-Sendo, A. Kozik, and I. Guevara-Lora, “Kinin Peptides Enhance Inflammatory  
1172 and Oxidative Responses Promoting Apoptosis in a Parkinson’s Disease Cellular Model,” *Mediators*  
1173 *Inflamm.*, vol. 2016, p. 4567343, 2016, doi: 10.1155/2016/4567343.
- 1174 [135] “ER Lipid Defects in Neuropeptidergic Neurons Impair Sleep Patterns in Parkinson’s Disease -  
1175 PubMed.” <https://pubmed.ncbi.nlm.nih.gov/29887339/> (accessed Aug. 21, 2021).
- 1176