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Pathophysiology of Non-Dopaminergic Monoamine Systems in Parkinson's Disease: Implications for Mood Dysfunction

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1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder affecting millions worldwide and is one of the most common diseases affecting the aging population (Delau et al., 2006). Clinical hallmarks of PD feature severe motor deficits characterized by bradykinesia, tremor, rigidity and postural instability. Though less recognized, PD symptoms also include psychiatric complications such as depression, anxiety and psychosis that deleteriously influence quality of life. While the origin of motor deficits is the progressive degeneration of nigrostriatal dopamine (DA) neurons, other monoamine neurons within the serotonin (5-HT) and norepinephrine (NE) system also degenerate, likely contributing to mood dysfunction. In this chapter the pathophysiology of non-dopaminergic monoamine systems, their contribution to PD-related mood dysfunction, and therapeutics targeting them will be discussed.

2. Norepinephrine system

In PD, the cardinal cell death of the dopaminergic substantia nigra pars compacta (SNpc) neurons is accompanied by deficits in other monoamine neurotransmitter systems. Of these, NE appears most consistently affected. Numerous studies, both neuroanatomical and biochemical, have documented severe loss of NE neurons, originating from the locus coeruleus (LC), concomitant with or even preceding the loss of DA neurons (Mann and Yates, 1983; Marien et al., 2004; Schapira et al., 2006). The precise anatomical relationship between the LC and the SNpc and the striatum remains to be elucidated; however, evidence exists for a functional relationship between these brain regions (Fornai et al., 2007). Most notable, loss of NE may exacerbate damage to the DA nigrostriatal system, as NE is postulated to play a neuroprotective and neuromodulator role in the progression of PD (Rommelfanger and Weinshenker, 2007). The following sections will focus on the pathophysiology of NE, its relative contribution to the development of psychiatric symptoms of PD, and the treatment of these symptoms using noradrenergic drugs.

2.1 CNS pathophysiology of NE system in PD

2.1.1 Neuroanatomical evidence in PD patients

As early as 1917, noradrenergic neurons originating from the LC were reported to be severely deteriorated in patients suffering from PD (Tretiakoff et al., 1917; Fornai et al.,

2007). In a landmark study by Hornykiewicz et al., (1960), direct biochemical evidence supported these initial findings, by showing the loss of both NE neurons and NE content in several brain regions in PD, including the caudate nucleus and putamen (Ehringer and Hornykiewicz, 1960).

Neuropathological evidence in post-mortem tissue of PD patients ranges from observation of Lewy bodies (LB) within single NE cells and cytoplasmic neurofibrillary tangles (NT) to a loss of neurons in the LC (Mann, 1983). Patt and Gerhard (1993), using a variant of the Golgi method, found that medium-sized LC neurons containing neuromelanin granules were most affected in PD patients (Patt and Gerhard, 1993) correlating with loss of synaptic spines, a reduction in dendritic length, swollen perikarya and apoptosis. Bertrand et al., (1997) reported the presence of glial proliferation along with extracellular neuromelanin granules around dying NE neurons. Post-mortem studies carried out in PD patients have established a loss of approximately 70% of NE neurons when compared to age-matched controls (Bertrand et al., 1997; Zarow et al., 2003). Interestingly, the NE neuronal loss was greater in the LC compared to cholinergic loss in the nucleus basalis and dopaminergic loss in the SNpc in Alzheimer and PD patients, respectively (Zarow et al., 2003). Of note, the loss of LC neurons observed in PD patients is not homogenous as there appears to be a disease specific and regional pattern to degeneration in the LC. For example, German and co-workers (1992) observed that in PD patients with no dementia complications, the degeneration was consistent throughout the rostral and caudal portion of the LC, whereas, in PD patients with dementia, the cell loss occurred more severely in the rostral portion of the LC nucleus. These findings have led to the postulation that LC degeneration patterns could be used to classify and differentiate between various sub-groups of PD patients. Comprehensive evidence by Braak and colleagues have found that, in PD patients, the degeneration of NE neurons progressed from lower brain stem regions, like the LC, to more rostral areas, like the SNpc (Braak and Braak, 2000; Braak et al., 2003).

Biochemical evidence obtained from post-mortem and ante-mortem studies in PD patients suggests that NE levels in multiple brain regions, including the motor cortex, hippocampus, striatum, substantia nigra and hypothalamus, are significantly decreased (Gesi et al., 2000). Interestingly, brain regions that are innervated by NE nuclei other than LC are relatively spared from NE loss.

Accumulating evidence strongly suggests that the loss of NE neurons originating from the LC is a very important aspect of the pathophysiology of PD and contributes to the progression of PD, deleteriously affecting the survival of DA neurons. For example, various experimental studies have demonstrated that prior loss of NE innervation increases the vulnerability of the DA neurons to a further neurotoxic insult (Fornai et al., 1995; Mavridis et al., 1991). Conversely, it has been established that increased NE stimulation is neuroprotective against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity (Kilbourn et al., 1998; Rommelfanger et al., 2004). Thus, it appears that NE may play a neurotrophic role acting as a neuroprotective mechanism for DA neurons. This was corroborated by Tong and colleagues (2006) who found an inverse relationship between intact NE innervation and DA loss in PD patients. Collectively, these findings suggest that the loss of LC neurons precedes and facilitates the subsequent damage to nigrostriatal DA neurons.

Therefore, since NE is known to act as a modulator of the dopaminergic system in various brain regions, the loss of NE appears to be a very critical event in the timeline of PD.

2.1.2 Mechanism(s) of NE loss

The mechanisms underlying NE loss like DA neurodegeneration remain to be elucidated. However, NE neurons are susceptible to the same insults that affect DA neurons such as oxidative stress, neuroinflammation, protein misfolding and neurotoxin-induced cell death. For example, Yavich et al. (2006) demonstrated that mice expressing a pathogenic mutation of α -synuclein have abnormal compartmentalization and metabolism of both DA and NE. In addition, it is well known that monoamines have a tendency to auto-oxidize leading to oxidative stress and neuronal cell loss (Chiueh et al., 2000; Maker et al., 1986); and the aforementioned abnormal compartmentalization of NE may make LC neurons vulnerable to oxidative stress. Genetic mutations in Parkin, a genotype found in PD, also make LC neurons vulnerable to cell death. Studies in mice have demonstrated that Parkin mutations lead to loss of LC neurons (Von Coelln et al., 2004) likely via protein misfolding and dysregulation of the ubiquitous-proteasome system. This is a compelling finding since alterations in the expression of proteasome activators have been shown to correlate with neuronal loss in SNpc and the LC. Poor expression of proteasome activators correlated with neuronal cell loss in the LC and regions expressing normal levels of the proteasome activators did not suffer from neuronal degeneration (McNaught et al., 2010). Finally, NE neurons are also susceptible to neurotoxin-induced apoptosis. For example, in the experimental 6-hydroxydopamine (6-OHDA) model of PD, administration of desipramine, a NE transporter (NET) inhibitor, infers protection to NE neurons. Since DA and NE transporters share homology in structure and display common affinity for several substrates, it is likely that NET takes up the same neurotoxins that affect DA neurons in sporadic PD. Collectively these factors could make the LC neurons vulnerable to damage in both genetic and sporadic models of PD. More studies that shed light on the neurodegenerative processes in the LC are necessary to better understand the progression of PD. Moreover, neuroprotective strategies directed toward LC neurons may be warranted since loss of LC neurons makes the DA neurons more vulnerable to neurodegeneration.

2.2 Non-motor symptoms

2.2.1 NE loss and non-motor symptoms

Although motor symptoms of PD are widely acknowledged hallmarks of this neurodegenerative disease, there exists compelling evidence for the presence of psychiatric complications, such as depression, anxiety and psychotic symptoms (Bosboom et al., 2004). Loss of dopaminergic and noradrenergic innervation has been associated with psychiatric complications such as depression (Remy et al., 2005) and anxiety (Stein et al., 1990; Lauterbach et al., 2003). Cognitive and mood dysfunction has been reported in >50% of PD patients. In patients with early PD, depression (40%), apathy (27%), and anxiety (27%) are widely reported (Aarsland et al., 2009) and it is notable that these non-motor symptoms are identified as the most important and devastating feature contributing towards poverty of quality of life (McKinlay et al., 2008; Schrag, 2006). Moreover, the incidence of depression and anxiety in PD exceeds not only rates within the normal population but also other neurological disorders (Weintraub et al., 2003), with anxiety disorders, such as off-period panic attacks and specific phobias, have been reported in nearly 40% of PD patients (Lauterbach, 2005). Collectively these findings lead to the important observation that depression and anxiety are likely a result of neuropathological processes rather than as a result of motor impairments.

The exact pathophysiology underlying these mood dysfunctions are unknown though given the role of NE in several of these symptoms, it is likely that NE loss in PD plays a critical role. As discussed earlier, neurodegeneration of LC neurons in PD is a well established phenomenon that precedes DA neuronal loss (Braak et al., 2003). It has been postulated that a compromised LC produces significant changes in NE receptors and transporters that may lead to the development or exacerbation of depression/anxiety (Eskow Jaunarajs et al., 2010). Additionally, Remy et al. (2005) have reported reduced binding for the DA/NE transporter, suggesting a loss of terminals, in the LC of PD patients suffering from anxiety and depression (Remy et al., 2005). In a rodent model of PD, alterations in DA and NE systems in the striatum have been reported to produce anxiety (Tadaiesky et al., 2008), consistent with findings in naïve rats that NE regulates anxiety behavior. Experimental studies have reported depression and anxiety-like behaviors in a 6-OHDA lesion model of PD (Branchi et al., 2010; Eskow Jaunarajs et al., 2010; Tadaiesky et al., 2008). Additionally, concomitant depletion of NE, 5-HT and DA in a unilateral rodent model of PD produced symptoms of depression, suggesting that loss of all three systems contribute to PD-like depression (Delaville et al., 2010). In an interesting study, Taylor et al. (2009) used a vesicular monoamine transporter-2 (VMAT-2) deficient mouse model to induce severe NE and DA loss thereby mimicking PD. VMAT-2 deficient mice exhibited severe depression and anxiety-like symptoms that worsened with advancing age (Taylor et al., 2009) highlighting a possible interplay between DA and NE. Histological studies have highlighted the fact that LC neuron morphology is more severely affected in PD with depression than in PD without depression (Chan-Palay and Asan, 1989). While most of the evidence in clinical and experimental models correlating NE deficit with mood dysfunction is indirect, there exists evidence that noradrenergic drugs might provide relief in the treatment of these mood disorders.

2.2.2 Treatment of non-motor symptoms with NE drugs

The role for the NE system in affective disorders such as anxiety and depression has been partially implicated by the effectiveness of drugs that enhance NE levels. Reboxetine, a NET inhibitor, has been proven to be effective in the treatment of depression associated with PD (Pintor et al., 2006). In one of the largest Randomized Clinical Trials (RCT) to date Menza and colleagues (2009) found that Nortryptaline, a tricyclic antidepressant (TCA), with preferential actions as a NET inhibitor, was proven to be more effective in treating depression in PD patients compared to selective 5-HT reuptake inhibitors (SSRIs: Menza et al., 2009). In a similar placebo controlled study in PD patients, Desipramine, a NET inhibitor, was found to be effective in treating depression; however, these improvements were accompanied with mild adverse side effects (Devos et al., 2008). These therapeutic findings suggest a more prominent role for NE in the development of depression in PD. The few drugs that seem to be effective in treating depression likely act to elevate extracellular NE levels in the brain, by blocking NET (Dziedzicka-Wasylewska et al., 2006). Therefore, it seems feasible that drugs that mimic NE or elevate NE levels in the brain would be effective in treating NE-related non-motor symptoms in PD.

3. Serotonin system

The 5-HT system like the NE system undergoes significant, though more variable, neurodegeneration as PD progresses; a finding documented in various studies, both post-

and ante-mortem (Miyawaki et al., 1997; Scatton et al., 1983). Since the 5-HT system ubiquitously innervates and modulates basal ganglia nuclei, 5-HT loss likely affects both motor symptoms of PD and l-DOPA related side effects. In addition, given the role of 5-HT in mood, such alterations may also correlate with the preponderance of depression and anxiety seen in PD. Therefore, various treatment strategies have been developed that modulate the 5-HT system. In the following sections, we review the neuropathology of the 5-HT system in PD, the consequences of a damaged 5-HT system on non-motor aspects, and the line of experimental and clinical treatments targeting the 5-HT system to provide symptomatic relief for the PD patient.

3.1 CNS pathophysiology of 5-HT system in PD

3.1.1 Neuroanatomical evidence in PD patients

Even though degeneration of DA neurons in the SNpc remains the best identified neuropathological hallmark in PD, there exists increasing evidence suggesting PD-related pathology in the principle 5-HT cell bodies, the raphe nuclei and other regions innervated by raphe neurons (Braak et al., 2003).

Multiple studies have reported the presence of LB in the caudal group of raphe nuclei, like the raphe magnus and raphe pallidus, in early PD, sometimes occurring even before the onset of motor symptoms (Braak et al., 2003; Del Tredici et al., 2002; Parkkinen et al., 2008). It is interesting to note that these caudal raphe nuclei contain 5-HT neurons associated with functions like pain perception, and gastrointestinal motility that are manifest as early symptoms in PD patients prior to motor complaints (Chaudhuri and Schapira, 2009). The rostral raphe nuclei consisting of dorsal and medial raphe nuclei are equally affected in PD and according to Braak staging, are affected before the SNpc but after the caudal raphe nuclei (Braak et al., 2003).

Despite reports of raphe LB formation, evidence for the degeneration of 5-HT neurons in the rostral raphe nuclei is variable; post-mortem analysis of PD brains by Paulus and Jellinger (1991) revealed a profound loss of 5-HT neurons, however, other studies have not (Halliday et al., 1990; Mann and Yates, 1983). Several studies have employed transcranial sonography to study the midbrain raphe nuclei. This work has revealed abnormal pathology in the form of hypoechogenicity or an absence of sonographic signals in PD vs. control subjects. Interestingly, PD patients in one study also suffered from higher incidence of depression, reflecting a direct relationship between raphe nuclei loss and PD-related depression (Becker et al., 1997; Berg and Gaenslen, 2010; Walter et al., 2007b). MRI imaging studies carried out in depressed PD patients have also demonstrated a loss of homogeneity in the midbrain raphe consistent with neuronal compromise and/or cell loss (Berg et al., 1999).

PD-related pathology of the 5-HT system is not limited to the cell bodies of the raphe nuclei. Convincing evidence exists for damaged 5-HT projections and terminals as well. For example, post-mortem studies in PD patients have described significant loss of 5-HT markers, such as brain 5-HT concentrations. In cortical and the basal ganglia regions 5-HT content has been reported to be reduced by as much as 50% compared to controls (Birkmayer and Birkmayer, 1987). Kish and colleagues (2008) investigated the integrity of the forebrain 5-HT system. In contrast to DA loss, which was preferential to the putamen, 5-HT loss was more prominent in the caudate for all 5-HT markers including 5-HT (-66%), the 5-HT metabolite 5-HIAA (-42%), 5-HT transporter (SERT), (-56%) and the rate limiting enzyme in 5-HT synthesis tryptophan hydroxylase (-59%). These corroborated ante-mortem

observations in PD patients that examined levels of 5-HIAA in cerebrospinal fluid and have found significant reductions when compared to control patients. Interestingly, the deficits in cerebrospinal fluid 5-HIAA levels were more pronounced in PD patients with depression in comparison to non-depressed PD patients, again supporting a relationship between decreased 5-HT function and depression in PD (Mayeux et al., 1984; Mayeux et al., 1986).

Development of additional imaging technologies, like PET and SPECT, has facilitated the measurement of SERT and thus the evaluation of the integrity of the 5-HT terminal (Meyer et al., 2007). In vivo SPECT studies, using non-specific ligands for SERT, found decreased binding in the cortex and hypothalamus of PD patients (Berding et al., 2003a; Berding et al., 2003b). However, these findings have been contradicted by studies that did not find any changes in the mid-brain but rather reduction in the thalamic nuclei of PD patients (Carette et al., 2008; Kim et al., 2003; Roselli et al., 2010). Decreased SERT binding has been observed by use of PET imaging using more specific ligands. Under these circumstances reduced SERT was observed in the striatum, frontal cortex, caudate nucleus, putamen and the mid-brain raphe region of patients with PD (Albin et al., 2008; Guttman et al., 2007; Kerenyi et al., 2003). SERT binding is also labile, changing as PD progresses. For example, in the early stages of PD, SERT binding has been shown to be reduced in only in the striatum, thalamus and cingulate cortex. In later symptomatic stages of PD these alterations appear to extend to the prefrontal cortex and the raphe nuclei (Haapaniemi et al., 2001; Politis et al., 2010). Such findings suggest that a progressive reduction in SERT binding may serve as good a bio-marker for the diagnosis and development of treatment strategies for PD patients.

In addition to neuronal integrity, 5-HT receptors are also affected in PD. Modification of pre- and post-synaptic 5-HT receptors has been observed in various animal and human studies of PD. While it is not clear whether these compensatory changes are due to lost 5-HT input, DA innervation, or DA replacement, it is established that dopaminergic tone regulates the expression of several 5-HT receptors. 5-HT_{1A} receptor binding is not consistently affected in the 6-OHDA model of PD; however, studies in MPTP-treated macaques suggest increases in striatal and cortical binding (Frechilla et al., 2001; Huot et al., 2010b). 5-HT_{1B} receptor binding is significantly increased in the striatum (54%) and the globus pallidus (33%). Intranigral lesions have also been reported to increase 5-HT₄ receptor density in the caudate and the globus pallidus (Di Matteo et al., 2008). Studies using in situ hybridization and autoradiographic radioligand binding have revealed few changes in 5-HT_{1A} and 5-HT_{2B} receptor binding (Numan et al., 1995; Zhang et al., 2008); however, 5-HT_{2A} receptors have been shown to increase in the striatum (Zhang et al., 2008). The possibility exists that striatal 5-HT_{2A} and 5-HT_{2C} receptor are differentially regulated in 6-OHDA-lesioned animals and the changes observed in these receptors could be a reflection of the compensatory changes in the PD-afflicted brain. Some of the changes in 5-HT receptor binding are reversible after treatment with l-DOPA, Zhang and colleagues (2008) reported a reversal of increased striatal 5-HT_{2A} receptor mRNA in a 6-OHDA rodent model of PD after l-DOPA treatment. Interestingly, l-DOPA did not alter the changes in striatal 5-HT_{2C} receptor mRNA levels. It appears that changes in regulation of the 5-HT_{2A} receptor are dependent on striatal DA levels and the 5-HT_{2C} loss could be due to nigrostriatal loss, thus reflecting a difference in regulation between the two receptor sub-types. The 5-HT receptor changes seen in PD patients are partly similar to changes in the experimental PD models. Similar increases were seen in the density of 5-HT_{2A} and 5-HT_{2C} receptor in the striatum as

well as other regions (Fox and Brotchie, 2000; Huot et al., 2010c; Radja et al., 1993). It is important to note that these changes may not be direct evidence of 5-HT neuropathology but definitely provide an insight into neuroplasticity of the 5-HT system that may unravel potential targets for therapeutic strategies in the treatment of PD.

An indirect marker for 5-HT alterations in PD is the assessment of responses to 5-HT challenge tests. Of these, the most common is the endocrine response to the 5-HT releasing agent, Fenfluramine. In normal subjects Fenfluramine produces robust increases in prolactin and corticosterone levels. However, in PD patients it was found that this endocrine response was impaired (Kostic et al., 1996; Volpi et al., 1997). Such effects may also correlate with non-motor symptoms since PD patients suffering from depression also displayed blunted prolactin responses in comparison to non-depressed PD patients (Kostic et al., 1996). Collectively these findings provide substantial evidence for neurochemical, neuroanatomical and functional alterations of the 5-HT system.

3.2 Non-motor symptoms

3.2.1 5-HT loss and non-motor symptoms

As previously mentioned depression and anxiety are some of the most common non-motor symptoms in PD and are even associated with an elevated risk towards the development of PD (Leentjens et al., 2003; Schuurman et al., 2002; Shiba et al., 2000). The underlying pathophysiological mechanisms remain to be completely understood; however, it is well established that 5-HT dysfunction plays an important role in several mood-disorders in non-PD patients (Michelsen et al., 2008). Depression not only reduces the quality of life for PD patients but has a negative effect on caregivers as well (Schrag et al., 2000; 2004).

During the progression of PD it has been observed that brain regions, like rostral raphe, thalamus and cortex, that mediate mood disturbances in PD are severely affected by the presence of Lewy bodies (Braak and Del Tredici, 2008). Currently, most evidence linking abnormal serotonergic neurotransmission to mood disturbances in PD is corroborative but points to a role for 5-HT pathology. For example, depressed PD patients display reduced brainstem raphe echogenicity, in comparison to non-depressed PD patients (Walter et al., 2007a). Post-mortem comparisons of neuronal density in the dorsal raphe nucleus between depressed and non-depressed PD patients found lower neuronal density in depressed PD patients (Paulus and Jellinger, 1991). In vivo studies measuring cerebrospinal fluid levels found lower levels of 5-HIAA in depressed PD patients indicating reduced 5-HT metabolism (Mayeux et al., 1986). Imaging studies have been less conclusive and have found either no change in SERT uptake (Kim et al., 2003) or reported elevated 5-HT receptor binding in depressed PD patients when compared to non-depressed PD patients (Boileau et al., 2008). Interestingly, acute tryptophan depletion in a small group of PD patients did not produce depression or anxiety in these patients (Leentjens et al., 2006). Another major non-motor symptom affecting PD patients is the development of psychosis that may lead to development of paranoid delusions in some PD patients (Ravina et al., 2007). The underlying cause remains to be elucidated and some investigators have postulated that there may be a serotonergic involvement. 5-HT₂ receptors, responsible for hallucinations and psychosis, are relatively intact or may even be upregulated in the cortex of PD patients suffering from psychosis compared to PD patients free from any psychotic disorder (Cheng et al., 1991; Huot et al., 2010a).

3.2.2 Treatment of non-motor symptoms with serotonergic drugs

Drugs acting on the serotonergic system are currently the standard of care for the treatment and management of psychiatric dysfunction, like anxiety, depression and psychosis in PD, despite causal evidence or 5-HT dysfunction in PD-related mood disorders. Most of the SSRIs currently used act by elevating the extracellular 5-HT levels and thus act indirectly on various post-synaptic 5-HT receptors, many of which have been implicated in mood disorders (Dobkin et al., 2011; Dobkin et al., 2010; Fox et al., 2009; Menza et al., 2009; Weintraub et al., 2006). The other potential side effects such as postural hypotension, sedation and 5-HT syndrome, due to 5-HT₁ receptor stimulation, continue to limit the use of these antidepressants in PD patients (Veazey et al., 2005). It is important to note that many PD patients suffer from orthostatic hypotension and tremors and these could get exacerbated. Nefazodone, a 5-HT₂ receptor antagonist/re-uptake inhibitor has been used as an antidepressant and to reduce extrapyramidal symptoms in PD patients (Avila et al., 2003).

Psychotic complications usually treated with drugs that have an anti-dopaminergic profile are not ideal for the PD patient since it can lead to worsening of motor symptoms. Therefore, atypical antipsychotics, like Clozapine and Quetiapine, have been found to be effective in treating psychosis in PD patients (Kurlan et al., 2007), an effect attributed to their 5-HT₂ receptor antagonistic properties. Another non-selective 5-HT₂ receptor antagonist Mianserin has been demonstrated to reduce visual hallucinations in a small group of PD patients without affecting the parkinsonian motor symptoms. Preliminary findings from a Phase II study evaluating Pimavanserin, a 5-HT_{2A} receptor inverse agonist, are encouraging and show a trend in improving psychosis without affecting PD motor scores (Meltzer et al., 2010).

It is of interest to note that L-DOPA therapy has been traditionally assumed to improve affective symptoms, like depression and anxiety; however, emerging evidence suggests that chronic use of L-DOPA may aggravate mood problems (Eskow Jaunarajs et al., 2011). Preclinical investigations have reported that 6-OHDA-lesioned rats chronically treated with L-DOPA exhibit reduced 5-HT and 5-HIAA levels (Carta et al., 2007; Eskow Jaunarajs et al., 2011). Studies employing in vivo microdialysis have confirmed reductions in 5-HT levels, after acute L-DOPA, in the 6-OHDA-lesioned striatum as well as in non-motor affective sites (Navailles et al., 2010). Chronic L-DOPA treatment has been demonstrated to reduce expression of tryptophan hydroxylase within the dorsal raphe nucleus, which may lead to reduced 5-HT synthesis and release in efferent structures (Eskow Jaunarajs et al., 2011). L-DOPA uptake and release of DA by 5-HT terminals into the striatum may compete with native 5-HT function leading to an aggravation of affective disorders like depression and anxiety in PD patients undergoing chronic L-DOPA therapy (Eskow Jaunarajs et al., 2011).

In sum, drugs acting on the serotonergic system provide some symptomatic relief for PD patients. However, L-DOPA therapy by itself has the potential to exacerbate mood disorders.

4. Conclusion

In conclusion, there exists convincing evidence that both 5-HT and NE systems are severely affected in PD and that they contribute towards PD progression and symptoms. Therapeutics targeting these systems appear beneficial; however, more research is necessary to develop more efficacious therapeutic targets and strategies.

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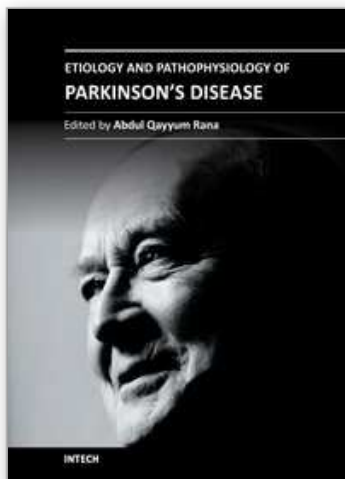
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This book about Parkinson's disease provides a detailed account of etiology and pathophysiology of Parkinson's disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinson's disease have been discussed in detail. This book can be used by basic scientists as well as researchers. Neuroscience fellows and life science readers can also obtain sufficient information. Beside genetic factors, other pathophysiological aspects of Parkinson's disease have been discussed in detail. Up to date information about the changes in various neurotransmitters, inflammatory responses, oxidative pathways and biomarkers has been described at length. Each section has been written by one or more faculty members of well known academic institutions. Thus, this book brings forth both clinical and basic science aspects of Parkinson's disease.

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