We are IntechOpen, the world’s leading publisher of Open Access books
Built by scientists, for scientists

4,000
Open access books available

116,000
International authors and editors

120M
Downloads

154
Countries delivered to

TOP 1%
Our authors are among the most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™
Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com
Pathophysiology of Non-Dopaminergic Monoamine Systems in Parkinson's Disease: Implications for Mood Dysfunction

Nirmal Bhide and Christopher Bishop
Department of Psychology, Binghamton University, Binghamton, NY USA

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 homogeneous 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 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 (Caretti 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-HTTA 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-HTTB receptor binding is significantly increased in the striatum (54%) and the globus pallidus (33%). Intranigral lesions have also been reported to increase 5-HTTA 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-HTTA and 5-HTTB receptor binding (Numan et al., 1995; Zhang et al., 2008); however, 5-HTTCA receptors have been shown to increase in the striatum (Zhang et al., 2008). The possibility exists that striatal 5-HTTCA and 5-HTTC 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-HTTCA 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-HTTC receptor mRNA levels. It appears that changes in regulation of the 5-HTTCA receptor are dependent on striatal DA levels and the 5-HTTC 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-HTTCA and 5-HTTC 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 serotoninergic 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-HT 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-HT2A 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.
5. References

Aarsland, D., Marsh, L., Schrag, A., 2009. Neuropsychiatric symptoms in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 24, 2175-86.

Albin, R.L., Koenig, A., Bohnen, N.I., Wernette, K., Kilbourn, M.A., Frey, K.A., 2008. Spared caudal brainstem SERT binding in early Parkinson's disease. Journal of cerebral blood flow and metabolism : official journal of the International Society of Cerebral Blood Flow and Metabolism. 28, 441-4.

Avila, A., Cardona, X., Martin-Baranera, M., Maho, P., Sastre, F., Bello, J., 2003. Does nefazodone improve both depression and Parkinson disease? A pilot randomized trial. Journal of clinical psychopharmacology. 23, 509-13.

Becker, T., Becker, G., Seufert, J., Hofmann, E., Lange, K.W., Naumann, M., Lindner, A., Reichmann, H., Riederer, P., Beckmann, H., Reiners, K., 1997. Parkinson's disease and depression: evidence for an alteration of the basal limbic system detected by transcranial sonography. Journal of neurology, neurosurgery, and psychiatry. 63, 590-6.

Berding, G., Brucke, T., Odin, P., Brooks, D.J., Kolbe, H., Gielow, P., Harke, H., Knoop, B.O., Dengler, R., Knapp, W.H., 2003a.[[123I]beta-CIT SPECT imaging of dopamine and serotonin transporters in Parkinson's disease and multiple system atrophy. Nuclear medicine. 42, 31-8.

Berding, G., Schrader, C.H., Peschel, T., van den Hoff, J., Kolbe, H., Meyer, G.J., Dengler, R., Knapp, W.H., 2003b. [N-methyl 11C]meta-Hydroxyephedrine positron emission tomography in Parkinson's disease and multiple system atrophy. European journal of nuclear medicine and molecular imaging. 30, 127-31.

Berg, D., Supprian, T., Hofmann, E., Zeiler, B., Jager, A., Lange, K.W., Reiners, K., Becker, T., 1999. Depression in Parkinson's disease: brainstem midline alteration on transcranial sonography and magnetic resonance imaging. Journal of neurology. 246, 1186-93.

Berg, D., Gaenslen, A., 2010. Place value of transcranial sonography in early diagnosis of Parkinson's disease. Neuro-degenerative diseases. 7, 291-9.

Bertrand, E., Lechowicz, W., Szpak, G.M., Dymecki, J., 1997. Qualitative and quantitative analysis of locus coeruleus neurons in Parkinson's disease. Folia neuropathologica / Association of Polish Neuropathologists and Medical Research Centre, Polish Academy of Sciences. 35, 80-6.

Birkmayer, J.G., Birkmayer, W., 1987. Improvement of disability and akinesia of patients with Parkinson's disease by intravenous iron substitution. Annals of clinical and laboratory science. 17, 32-5.

Bosboom, J.L., Stoffers, D., Wolters, E., 2004. Cognitive dysfunction and dementia in Parkinson's disease. Journal of neural transmission. 111, 1303-15.

Braak, H., Braak, E., 2000. Pathoanatomy of Parkinson's disease. Journal of neurology. 247 Suppl 2, Iii-10.

Braak, H., Del Tredici, K., Rub, U., de Vos, R.A., Jansen Steur, E.N., Braak, E., 2003. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of aging. 24, 197-211.

Braak, H., Del Tredici, K., 2008. Invited Article: Nervous system pathology in sporadic Parkinson disease. Neurology. 70, 1916-25.
Etiology and Pathophysiology of Parkinson's Disease

Branchi, I., D'Andrea, I., Armida, M., Carnevale, D., Ajmone-Cat, M.A., Pezzola, A., Potenza, R.L., Morgese, M.G., Cassano, T., Minghetti, L., Popoli, P., Alleva, E., 2010. Striatal 6-OHDA lesion in mice: Investigating early neurochemical changes underlying Parkinson's disease. Behavioural brain research. 208, 137-43.

Caretti, V., Stoffers, D., Winogrodzka, A., Isaías, I.U., Costantino, G., Pezzoli, G., Ferrarese, C., Antonini, A., Wolters, E.C., Booij, J., 2008. Loss of thalamic serotonin transporters in early drug-naive Parkinson's disease patients is associated with tremor: an [(123)I]beta-CIT SPECT study. Journal of neural transmission. 115, 721-9.

Carta, M., Carlsson, T., Kirik, D., Bjorklund, A., 2007. Dopamine released from 5-HT terminals is the cause of L-DOPA-induced dyskinesia in parkinsonian rats. Brain : a journal of neurology. 130, 1819-33.

Chaudhuri, K.R., Schapira, A.H., 2009. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet neurology. 8, 464-74.

Chaudhuri, K.R., Schapira, A.H., 2009. Non-motor symptoms of Parkinson's disease: dopaminergic pathophysiology and treatment. Lancet neurology. 8, 464-74.

Chan-Palay, V., Asan, E., 1989. Alterations in catecholamine neurons of the locus coeruleus in senile dementia of the Alzheimer type and in Parkinson's disease with and without dementia and depression. Journal of comparative neurology. 287, 373-392.

Chiueh, C.C., Andoh, T., Lai, A.R., Lai, E., Krishna, G., 2000. Neuroprotective strategies in Parkinson's disease: protection against progressive nigral damage induced by free radicals. Neurotoxicity research. 2, 293-310.

Del Tredici, K., Rub, U., De Vos, R.A., Bohl, J.R., Braak, H., 2002. Where does parkinson disease pathology begin in the brain? Journal of neuropathology and experimental neurology. 61, 413-26.

Delaville, C., Chetrit, J., Abdallah, K., Morin, S., Cardoit, L., De Deurwaerdere, P., Benzazzouz, A. 2010. Involvement of monoamine deficiency in motor and nonmotor disabilities in Parkinson's disease: behavioral, bicochemical and electrophysiological studies. International Basal Ganglia Society abstract

Di Matteo, V., Pierucci, M., Esposito, E., Crescimanno, G., Benigno, A., Di Giovanni, G., 2008. Serotonin modulation of the basal ganglia circuitry: therapeutic implication for Parkinson's disease and other motor disorders. Progress in brain research. 172, 423-63.

Dobkin, R.D., Menza, M. Bienfait, K.L., Gara, M., Marin, H., Mark, M.H., Dicke, A., Troster, A. 2010. The impact of antidepressant treatment on cognitive functioning in depressed patients with Parkinson's disease. Journal of neuropsychiatry and neurological sciences. 22(2), 188-95.

Dobkin, R.D., Menza, M. Bienfait, K.L., Gara, M., Marin, H., Mark, M.H., Dicke, A., Friedman, J. 2011. Depression in Parkinson's disease: symptom improvement and residual symptoms after acute pharmacologic management. American journal of Geriatric Psychiatry. 19(3), 222-9.

Devos, D., Dujardin, K., Poiriot, I., Moreau, C., Cottencin, O., Thomas, P., Destee, A., Bordet, R., Defebvre, L. 2008. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Movement Disorders.23 (6), 850-857.
Pathophysiology of Non-Dopaminergic Monoamine Systems in Parkinson's Disease: Implications for Mood Dysfunction

Ehringer, H., Hornykiewicz, O., 1960. [Distribution of noradrenaline and dopamine (3-hydroxytyramine) in the human brain and their behavior in diseases of the extrapyramidal system]. Klinische Wochenschrift. 38, 1236-9.

Eskow Jaunarajs, K.L., Dupre, K.B., Ostock, C.Y., Button, T., Deak, T., Bishop, C., 2010. Behavioral and neurochemical effects of chronic L-DOPA treatment on nonmotor sequelae in the hemiparkinsonian rat. Behavioural pharmacology. 21, 627-37.

Eskow Jaunarajs, K.L., Angoa-Perez, M., Kuhn, D.M., Bishop, C., 2011. Potential mechanisms underlying anxiety and depression in Parkinson's disease: consequences of L-DOPA treatment. Neuroscience and biobehavioral reviews. 35, 556-64.

Fornai, F., Bassi, L., Torracca, M.T., Scalori, V., Corsini, G.L., 1995. Noradrenaline loss exacerbates methamphetamine-induced striatal dopamine depletion in mice. European journal of pharmacology. 283, 99-102.

Fornai, F., di Poggio, A.B., Pellegrini, A., Ruggieri, S., Paparelli, A., 2007. Noradrenaline in Parkinson's disease: from disease progression to current therapeutics. Current medicinal chemistry. 14, 2330-4.

Fox, S.H., Brotchie, J.M., 2000. 5-HT2C receptor binding is increased in the substantia nigra pars reticulata in Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 15, 1064-9.

Fox, S.H., Chuang, R., Brotchie, J.M., 2009. Serotonin and Parkinson's disease: On movement, mood, and madness. Movement disorders : official journal of the Movement Disorder Society. 24, 1255-66.

Frechilla, D., Cobreros, A., Saldise, L., Moratalla, R., Insauti, R., Luquin, M., Del Rio, J., 2001. Serotonin 5-HT(1A) receptor expression is selectively enhanced in the striosomal compartment of chronic parkinsonian monkeys. Synapse. 39, 288-96.

German, D.C., Manaye, K.F., White, C.L., 3rd, Woodward, D.J., McIntire, D.D., Smith, W.K., Kalaria, R.N., Mann, D.M., 1992. Disease-specific patterns of locus coeruleus cell loss. Annals of neurology. 32, 667-76.

Gesi, M., Soldani, P., Giorgi, F.S., Santinami, A., Bonaccorsi, I., Fornai, F., 2000. The role of the locus coeruleus in the development of Parkinson's disease. Neuroscience and biobehavioral reviews. 24, 655-68.

Guttman, M., Boileau, I., Warsh, J., Saint-Cyr, J.A., Ginovart, N., McCluskey, T., Houle, S., Wilson, A., Mundo, E., Rusjan, P., Meyer, J., Kish, S.J., 2007. Brain serotonin transporter binding in non-depressed patients with Parkinson's disease. European journal of neurology : the official journal of the European Federation of Neurological Societies. 14, 523-8.

Haapaniemi, T.H., Ahonen, A., Torniainen, P., Sotaniemi, K.A., Myllyla, V.V., 2001. [123I]beta-CIT SPECT demonstrates brain dopamine and serotonin transporter levels in untreated parkinsonian patients. Movement disorders : official journal of the Movement Disorder Society. 16, 124-30.

Halliday, G.M., Li, Y.W., Blumbergs, P.C., Joh, T.H., Cotton, R.G., Howe, P.R., Blessing, W.W., Geffen, L.B., 1990. Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. Annals of neurology. 27, 373-85.

Hein, L., Altman, J.D., Kobilka, B.K., 1999. Two functionally distinct alpha2-adrenergic receptors regulate sympathetic neurotransmission. Nature. 402, 181-4.
Huot, P., Johnston, T.H., Darr, T., Hazrati, L.N., Visanji, N.P., Pires, D., Brotchie, J.M., Fox, S.H., 2010a. Increased 5-HT(2A) receptors in the temporal cortex of parkinsonian patients with visual hallucinations. Movement disorders. 25(10), 1399-1408.

Huot, P., Johnston, T.H., Koprich, J.B., Winkelmolen, L., Fox, S.H., Brotchie, J.M., 2010b. Regulation of cortical and striatal 5-HT(1A) receptors in the MPTP-lesioned macaque. Neurobiology of aging.

Huot, P., Johnston, T.H., Winkelmolen, L., Fox, S.H., Brotchie, J.M., 2010c. 5-HT(2A) receptor levels increase in MPTP-lesioned macaques treated chronically with L-DOPA. Neurobiology of aging.

Jackson, M.J., Al-Barghouthy, G., Pearce, R.K., Smith, L., Hagan, J.J., Jenner, P., 2004. Effect of 5-HT1B/D receptor agonist and antagonist administration on motor function in haloperidol and MPTP-treated common marmosets. Pharmacology, biochemistry, and behavior. 79, 391-400.

Kerenyi, L., Ricaurte, G.A., Schretlen, D.J., McCann, U., Varga, J., Mathews, W.B., Ravert, H.T., Dannals, R.F., Hilton, J., Wong, D.F., Szabo, Z., 2003. Positron emission tomography of striatal serotonin transporters in Parkinson disease. Archives of neurology. 60, 1223-9.

Kilbourn, M.R., Sherman, P., Abbott, L.C., 1998. Reduced MPTP neurotoxicity in striatum of the mutant mouse tottering. Synapse. 30, 205-10.

Kim, S.E., Choi, J.Y., Cho, Y.S., Choi, Y., Lee, W.Y., 2003. Serotonin transporters in the midbrain of Parkinson's disease patients: a study with 123I-beta-CIT SPECT. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 44, 870-6.

Kish, S.J., Tong, J., Hornykiewicz, O., Rajput, A., Chang, L.J., Guttman, M., Furukawa, Y., 2008. Preferential loss of serotonin markers in caudate versus putamen in Parkinson's disease. Brain : a journal of neurology. 131, 120-31.

Kostic, V.S., Lecic, D., Doder, M., Marinkovic, J., Filipovic, S., 1996. Prolactin and cortisol responses to fenfluramine in Parkinson's disease. Biological psychiatry. 40, 769-75.

Kurlan, R., Cummings, J., Raman, R., Thal, L., 2007. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. Neurology. 68, 1356-63.

Lauterbach, E.C., Freeman, A., and Vogel, R.L. 2003. Correlates of generalized anxiety and panic attacks in dystonia and Parkinson's disease. Cognitive and behavioral neurology. 16, 225-233.

Lauterbach, E.C., 2005. The neuropsychiatry of Parkinson's disease. Minerva medica. 96(3), 155-173.

Leentjens, A.F., Van den Akker, M., Metsemakers, J.F., Lousberg, R., Verhey, F.R., 2003. Higher incidence of depression preceding the onset of Parkinson's disease: a register study. Movement disorders : official journal of the Movement Disorder Society. 18, 414-8.

Leentjens, A.F., Scholtes, B., Vreeling, F.W., Verhey, F.R., 2006. The serotonergic hypothesis for depression in Parkinson's disease: an experimental approach. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 31, 1009-15.

Maker, H.S., Weiss, C., Brannan, T.S., 1986. Amine-mediated toxicity. The effects of dopamine, norepinephrine, 5-hydroxytryptamine, 6-hydroxydopamine, ascorbate,
glutathione and peroxide on the in vitro activities of creatine and adenylate kinases in the brain of the rat. Neuropharmacology. 25, 25-32.

Mann, D.M., 1983. The locus coeruleus and its possible role in ageing and degenerative disease of the human central nervous system. Mechanisms of ageing and development. 23, 73-94.

Mann, D.M., Yates, P.O., 1983. Pathological basis for neurotransmitter changes in Parkinson's disease. Neuropathology and applied neurobiology. 9, 3-19.

Marien, M.R., Colpaert, F.C., Rosenquist, A.C., 2004. Noradrenergic mechanisms in neurodegenerative diseases: a theory. Brain research. Brain research reviews. 45, 38-78.

Marin, C., Aguilar, E., Rodriguez-Oroz, M.C., Bartoszyk, G.D., Obeso, J.A., 2009. Local administration of sarizotan into the subthalamic nucleus attenuates levodopa-induced dyskinesias in 6-OHDA-lesioned rats. Psychopharmacology. 204, 241-50.

Mavridis, M., Degryse, A.D., Lategian, A.J., Marien, M.R., Colpaert, F.C., 1991. Effects of locus coeruleus lesions on parkinsonian signs, striatal dopamine and substantia nigra cell loss after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in monkeys: a possible role for the locus coeruleus in the progression of Parkinson's disease. Neuroscience. 41, 507-23.

Mayeux, R., Williams, J.B., Stern, Y., Cote, L., 1984. Depression and Parkinson's disease. Advances in neurology. 40, 241-50.

Mayeux, R., Stern, Y., Williams, J.B., Cote, L., Frantz, A., Dyrenfurth, I., 1986. Clinical and biochemical features of depression in Parkinson's disease. The American journal of psychiatry. 143, 756-9.

McKinlay, A., Grace, R.C., Dalrymple-Alford, J.C., Anderson, T., Fink, J., Roger, D., 2008. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. Parkinsonism & related disorders. 14, 37-42.

McNaught, K.S., Jnobaptiste, R., Jackson, T., Jengelley, T.A., 2010. The pattern of neuronal loss and survival may reflect differential expression of proteasome activators in Parkinson's disease. Synapse. 64, 241-50.

Meltzer, H.Y., Mills, R., Revell, S., Williams, H., Johnson, A., Bahr, D., Friedman, J.H., 2010. Pimavanserin, a serotonin(2A) receptor inverse agonist, for the treatment of Parkinson's disease psychosis. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 35, 881-92.

Menza, M., Dobkin, R.D., Marin, H., Mark, M.H., Gara, M., Buyske, S., Bienfait, K., Dicke, A., 2009. A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology. 72, 886-92.

Meyer, J.S., Huang, J., Chowdhury, M.H., 2007. MRI confirms mild cognitive impairments prodromal for Alzheimer's, vascular and Parkinson-Lewy body dementias. Journal of the neurological sciences. 257, 97-104.

Michelsen, K.A., Prickaerts, J., Steinbusch, H.W., 2008. The dorsal raphe nucleus and serotonin: implications for neuroplasticity linked to major depression and Alzheimer's disease. Progress in brain research. 172, 233-64.

Miyawaki, E., Meah, Y., Koller, W.C., 1997. Serotonin, dopamine, and motor effects in Parkinson's disease. Clinical neuropharmacology. 20, 300-10.
Navailles, S., Bioulac, B., Gross, C., De Deurwaerdere, P., 2010. Serotonergic neurons mediate ectopic release of dopamine induced by L-DOPA in a rat model of Parkinson's disease. Neurobiology of disease. 38, 136-43.

Numan, S., Lundgren, K.H., Wright, D.E., Herman, J.P., Seroogy, K.B., 1995. Increased expression of 5HT2 receptor mRNA in rat striatum following 6-OHDA lesions of the adult nigrostriatal pathway. Brain research. Molecular brain research. 29, 391-6.

Parkkinnen, L., Pirttila, T., Alafuzoff, I., 2008. Applicability of current staging/categorization of alpha-synuclein pathology and their clinical relevance. Acta neuropathologica. 115, 399-407.

Patt, S., Gerhard, L., 1993. A Golgi study of human locus coeruleus in normal brains and in Parkinson's disease. Neuropathology and applied neurobiology. 19, 519-23.

Paulus, W., Jellinger, K., 1991. The neuropathologic basis of different clinical subgroups of Parkinson's disease. Journal of neuropathology and experimental neurology. 50, 743-55.

Pintor, L., Bailles, E., Valldeoriola, F., Tolosa, E., Marti, M.J., de Pablo, J., 2006. Response to 4-month treatment with reboxetine in Parkinson's disease patients with a major depressive episode. General hospital psychiatry. 28, 59-64.

Politis, M., Wu, K., Loane, C., Turkheimer, F.E., Molloy, S., Brooks, D.J., Piccini, P., 2010. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. Neurology. 75, 1920-7.

Radja, F., Descarries, L., Dewar, K.M., Reader, T.A., 1993. Serotonin 5-HT1 and 5-HT2 receptors in adult rat brain after neonatal destruction of nigrostriatal dopamine neurons: a quantitative autoradiographic study. Brain research. 606, 273-85.

Ravina, B., Camicioli, R., Como, P.G., Marsh, L., Jankovic, J., Weintraub, D., Elm, J., 2007. The impact of depressive symptoms in early Parkinson disease. Neurology. 69, 342-7.

Remy, P., Doder, M., Lees, A., Turjanski, N., Brooks, D., 2005. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain : a journal of neurology. 128, 1314-22.

Richard, I.H., Schiffer, R.B., Kurlan, R., 1996. Anxiety and Parkinson's disease. The Journal of neuropsychiatry and clinical neurosciences. 8, 383-92.

Rommelfanger, K.S., Weinsenker, D., Miller, G.W., 2004. Reduced MPTP toxicity in noradrenaline transporter knockout mice. Journal of neurochemistry. 91, 1116-24.

Rommelfanger, K.S., Weinsenker, D., 2007. Noradrenaline: The redheaded stepchild of Parkinson's disease. Biochemical pharmacology. 74, 177-90.

Roselli, F., Pisciotta, N.M., Pennelli, M., Aniello, M.S., Gigante, A., De Caro, M.F., Ferrannini, E., Tartaglione, B., Niccoli-Asabella, A., Defazio, G., Livrea, P., Rubini, G., 2010. Midbrain SERT in degenerative parkinsonisms: a 123I-FP-CIT SPECT study. Movement disorders : official journal of the Movement Disorder Society. 25, 1853-9.

Scatton, B., Javoy-Agid, F., Rouquier, L., Dubois, B., Agid, Y., 1983. Reduction of cortical dopamine, noradrenaline, serotonin and their metabolites in Parkinson's disease. Brain research. 275, 321-8.

Schapira, A.H., Bezard, E., Brochotie, J., Calon, F., Collingridge, G.L., Fenger, B., Hengerer, B., Hirsch, E., Jenner, P., Le Novere, N., Obeso, J.A., Schwarzschild, M.A., Spampinato, U., Davids, G., 2006. Novel pharmacological targets for the treatment of Parkinson's disease. Nature reviews. Drug discovery. 5, 845-54.
Schrag, A., Jahanshahi, M., Quinn, N., 2000. What contributes to quality of life in patients with Parkinson's disease? Journal of neurology, neurosurgery, and psychiatry. 69, 308-12.

Schrag, A., Morley, D., Quinn, N., Jahanshahi, M., 2004. Impact of Parkinson's disease on patients' adolescent and adult children. Parkinsonism & related disorders. 10, 391-7.

Schrag, A., 2006. Quality of life and depression in Parkinson's disease. Journal of the neurological sciences. 248, 151-7.

Schuurman, A.G., van den Akker, M., Ensinck, K.T., Metsemakers, J.F., Knoottnerus, J.A., Leentjens, A.F., Buntinx, F., 2002. Increased risk of Parkinson's disease after depression: a retrospective cohort study. Neurology. 58, 1501-4.

Shiba, M., Bower, J.H., Maraganore, D.M., McDonnell, S.K., Peterson, B.J., Ahlskog, J.E., Schaid, D.J., Rocca, W.A., 2000. Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Movement disorders : official journal of the Movement Disorder Society. 15, 669-77.

Stein, M.B., Heuser, I.J., Juncos, J.L., and Uhde, T.W. 1990. Anxiety disorders in patients with Parkinson's disease. American journal of psychiatry. 41, 1086-1089.

Tadaiesky, M.T., Dombrowski, P.A., Figueiredo, C.P., Cargnin-Ferreira, E., Da Cunha, C., Takahashi, R.N., 2008. Emotional, cognitive and neurochemical alterations in a premotor stage model of Parkinson's disease. Neuroscience. 156, 830-40.

Taylor, T.N., Caudle, W.M., Shepherd, K.R., Noorian, A., Jackson, C.R., Iuvone, P.M., Weinschenker, D., Greene, J.G., Miller, G.W., 2009. Nonmotor symptoms of Parkinson's disease revealed in an animal model with reduced monoamine storage capacity. The Journal of neuroscience : the official journal of the Society for Neuroscience. 29, 8103-13.

Veazey, C., Aki, S.O., Cook, K.F., Lai, E.C., Kunik, M.E., 2005. Prevalence and treatment of depression in Parkinson's disease. The Journal of neuropsychiatry and clinical neurosciences. 17, 310-23.

Volpi, R., Caffarra, P., Boni, S., Scaglioni, A., Malvezzi, L., Saginario, A., Chiodera, P., Cairo, V., 1997. ACTH/cortisol involvement in the serotonergic disorder affecting the parkinsonian brain. Neuropsychobiology. 35, 73-8.

Von Coelln, R., Thomas, B., Savitt, J.M., Lim, K.L., Sasaki, M., Hess, E.J., Dawson, V.L., Dawson, T.M., 2004. Loss of locus coeruleus neurons and reduced startle in parkin null mice. Proceedings of the National Academy of Sciences of the United States of America. 101, 10744-9.

Walter, U., Dressler, D., Wollters, A., Benecke, R., 2007a. Transcranial brain sonography findings in clinical subgroups of idiopathic Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 22, 48-54.

Walter, U., Hoeppner, J., Prudente-Morrissey, L., Horowski, S., Herpertz, S.C., Benecke, R., 2007b. Parkinson's disease-like midbrain sonography abnormalities are frequent in depressive disorders. Brain : a journal of neurology. 130, 1799-807.

Weintraub, D., Morales, K.H., Moberg, P.J., Bilker, W.B., Balderston, C., Duda, J.E., Katz, I.R., Stern, M.B., 2005. Antidepressant studies in Parkinson's disease: a review and meta-analysis. Movement disorders : official journal of the Movement Disorder Society. 20, 1161-9.
Zarow, C., Lyness, S.A., Mortimer, J.A., Chui, H.C., 2003. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. Archives of neurology. 60, 337-41.

Zhang, X., Andren, P.E., Greengard, P., Svenningsson, P., 2008. Evidence for a role of the 5-HT1B receptor and its adaptor protein, p11, in L-DOPA treatment of an animal model of Parkinsonism. Proceedings of the National Academy of Sciences of the United States of America. 105, 2163-8.
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.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Nirmal Bhide and Christopher Bishop (2011). Pathophysiology of Non-Dopaminergic Monoamine Systems in Parkinson's Disease: Implications for Mood Dysfunction, Etiology and Pathophysiology of Parkinson’s Disease, Prof. Abdul Qayyum Rana (Ed.), ISBN: 978-953-307-462-7, InTech, Available from: http://www.intechopen.com/books/etiology-and-pathophysiology-of-parkinson-s-disease/pathophysiology-of-non-dopaminergic-monoamine-systems-in-parkinson-s-disease-implications-for-mood-d
