Published in final edited form as:

Neurobiol Dis. 2012 June ; 46(3): 597–606. doi:10.1016/j.nbd.2011.12.040.

Animal models of the non-motor features of Parkinson's disease

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Abstract

The non-motor symptoms (NMS) of Parkinson's disease (PD) occur in roughly 90% of patients, have a profound negative impact on their quality of life, and often go undiagnosed. NMS typically involve many functional systems, and include sleep disturbances, neuropsychiatric and cognitive deficits, and autonomic and sensory dysfunction. The development and use of animal models have provided valuable insight into the classical motor symptoms of PD over the past few decades. Toxin-induced models provide a suitable approach to study aspects of the disease that derive from the loss of nigrostriatal dopaminergic neurons, a cardinal feature of PD. This also includes some NMS, primarily cognitive dysfunction. However, several NMS poorly respond to dopaminergic treatments, suggesting that they may be due to other pathologies. Recently developed genetic models of PD are providing new ways to model these NMS and identify their mechanisms. This review summarizes the current available literature on the ability of both toxin-induced and genetically-based animal models to reproduce the NMS of PD.

Keywords

Rats; Mice; Non-human primates

An updated view of an old mystery: The non-motor symptoms of Parkinson's disease

Parkinson's disease (PD) was first described as the 'shaking palsy' by James Parkinson in 1817 and its etiology continues to be the focus of intense clinical and scientific study. This incurable and debilitating neurodegenerative disease currently affects over a million people in the United States alone and totals to about four million cases worldwide (Dorsey et al., 2007; Fahn S, 2010). The diagnosis of PD is based on motor impairments manifested as resting tremor, muscle rigidity, bradykinesia and postural instability. These symptoms are primarily due to a 50 to 70% loss of dopamine (DA) neurons in the substantia nigra pars compacta (SNpc), a pathological hallmark of the disease (Fearnley and Lees, 1991). Following the work of Carlsson et al. (1957), replacement of DA via administration of 3,4-Dihydroxyphenylalanine (L-DOPA) has remained the most common and effective treatment for patients (Vlaar et al., 2011). L-DOPA treatment usually improves motor functioning and is associated with a drop in mortality levels (Rajput, 2001), but side effects, primarily drug-induced dyskinesia, can severely reduce treatment benefits. The availability of direct DA agonists and modifiers of DA metabolism, as well as deep brain stimulation, have helped improve the symptomatic treatment of the cardinal motor symptoms of PD (Bronstein et al.,

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2011; Factor, 2008). However, there are multiple debilitating symptoms that are not responsive to DAergic treatments, including some motor disturbances (freezing and postural instability) and most non-motor symptoms (NMS) of PD (Wolters, 2009). Several of these NMS were described in James Parkinson's original essay. They can include sleep disturbances, neuropsychiatric and cognitive deficits, and autonomic and sensory dysfunction (Bassetti, 2011; Chaudhuri et al., 2011). Further highlighting their importance, retrospective studies showed that some NMS, can appear several years before the onset of the classical motor signs (Abbott et al., 2005, 2007; Ross et al., 2006). Importantly, patients report that NMS have an even greater negative impact on their quality of life than the motor aspects of the disease (Martinez-Martin, 2011). Despite increased awareness of the importance of NMS, frequent symptoms such as constipation, depression and daytime sleepiness go undiagnosed and untreated in roughly 50% of cases (Shulman et al., 2002; Sullivan et al., 2007; Thompson et al., 2011).

As clinicians continued to identify PD symptoms that were unresponsive to L-DOPA treatment, the importance of extranigral dysfunction and degeneration became evident. It is well established that the extrapyramidal motor features of the disease are due to nigrostriatal degeneration. However, *extranigral* changes in the enteric, peripheral, and central nervous system likely contribute to the heterogeneity of the NMS observed in PD (Halliday et al., 2011; Lim et al., 2009). Olfactory dysfunction, which frequently precedes the onset of motor symptoms, is present in the majority of PD patients and may be due to nondopaminergic degeneration of the olfactory bulb and other related nuclei (Braak et al., 2003; Ross et al., 2008). Gastrointestinal disturbances, including constipation and delayed gastric emptying, are also part of the prodromal NMS (Savica et al., 2009), and the pathology in the enteric system is thought to be a mechanism for their development (Braak et al., 2006). Disturbances in sleep are another common early NMS; in fact, REM behavioral disorder engenders an increased risk for the subsequent development of PD (Iranzo et al., 2006). Changes to multiple neurotransmitter systems of the brainstem have been reported and could contribute to these sleep anomalies (Boeve et al., 2007). Depression may be secondary to the pathology observed in the locus coeruleus and raphe nuclei, which provide noradrenergic and serotonergic innervation to the cerebral cortex and limbic system, respectively, is another NMS that can appear early in the progression of PD (Paulus and Jellinger, 1991). Orthostatic hypotension is associated with the duration and severity of PD (Oka et al., 2007), although the presence of this symptom during the early stages of the disease suggests an atypical parkinsonism (Ha et al., 2011). This autonomic dysfunction may be related to degeneration of the sympathetic cardiac and vasomotor systems (Oka et al., 2007). Multiple cognitive deficits are frequent at early stages of PD and may be associated with changes in dopaminergic and cholinergic systems (Kehagia et al., 2010). However, dementia characterized by visuo-spatial deficits and dysexecutive syndrome is usually associated with late stages of disease and has been correlated with the extension of Lewy Body pathology to the cerebral cortex (Padovani et al., 2006). The extent of neuronal loss in extranigral brain regions, including the dorsal motor nucleus of the vagus nerve, locus coeruleus, amygdala, and the neocortex varies in post-mortem studies (Halliday et al., 1990; Harding et al., 2002; Pedersen et al., 2005; Perl, 2007). However, neuropathological studies by Braak and others suggest a potential mechanism, other than overt neuronal loss, that may explain the multiplicity and early appearance of NMS in PD. The Braak staging system defines the progression of pathological changes in PD based on the distribution of alpha-synuclein (aSyn) pathology in Lewy neurites and Lewy bodies (Braak et al., 2003). According to this view, the earliest pathological changes in the brain occur in the medulla oblongata and olfactory bulb (Braak stages I and II). As the disease progresses, Lewy pathology can be found in the gray matter nuclei of the midbrain, followed by the substantia nigra and the basal forebrain (Braak stages III and IV). It is not until stage IV that patients start to manifest the classical motor symptoms of PD. Lewy bodies appear in the neocortex (Braak

stages V and VI) as the disease worsens (Dickson et al., 2010; Hawkes et al., 2010). Lewy bodies have also been found in the enteric nervous system (Wakabayashi et al., 1989) and it is possible that the pathology of PD begins in the gut and olfactory systems (Braak et al., 2006). Although challenged by some authors (Jellinger, 2009; Kingsbury et al., 2010), Braak's staging provides a neuroanatomical substrate for the broad range of symptoms displayed by patients suffering from PD and provides a framework for modeling these disturbances in animals.

Unquestionably, the development and use of animal models have provided valuable insight into the classical motor symptoms of PD. Toxin-induced lesions of the nigrostriatal DAergic neurons that have been used to model PD since the 1960s have recently been reevaluated for their ability to model some NMS. In addition, based on the progression of the pathology of PD, efforts have begun to shift away from models that induce rapid destruction of the vast majority of the DA cells of the SNpc to more gradual and broader models that allow for the analysis of the earlier stages, and the NMS, of PD (Table 1).

The non-motor features of toxin-induced parkinsonism

The discovery that a loss of nigrostriatal DA neurons is central to the neuropathology of PD (Carlsson, 1972) and the subsequent finding that environmental factors may be associated with PD have led to the creation of multiple animal models designed to study the loss of DA neurons and its consequence for the basal ganglia motor circuit. Some of the most widely used toxins to study PD in animals include 6-hydroxydopamine (6-OHDA), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone and paraquat. Ever since 6-OHDA was found to have deleterious effects on catecholamine containing cells (Ungerstedt, 1968), it was extensively used to target the nigrostriatal pathway via stereotactic injections in an attempt to mimic the parkinsonian motor symptoms (Chesselet and Delfs, 1996; Perese et al., 1989). MPTP was discovered when a group of young men presented with parkinsonism after being exposed to a batch of 'synthetic heroin' that was contaminated with this toxic compound (Langston et al., 1999). MPTP metabolizes to the 1-methyl-4-phenyl-2,3-dihydropyridinium ion (MPP⁺) which enters dopaminergic neurons and once in the cell inhibits mitochondrial complex I to produce oxidative stress and cell death (Javitch et al., 1985; Nicklas et al., 1985). Another toxin found to be linked to PD is the pesticide rotenone, which is also a complex I inhibitor but does not specifically accumulate in DAergic cells (Betarbet et al., 2000; Ferrante et al., 1997; Zhu et al., 2004).

The popularity of these toxins rests mainly on their ability to mimic dramatic loss of the nigrostriatal DAergic neurons, resulting in some of the motor features of PD (Feger et al., 2002; Jenner, 2008). These toxins have also provided an essential tool for developing animal models that are useful to test the efficacy of anti-parkinsonian treatments (Jenner, 2009; Schwarting and Huston, 1996). However, the usefulness of these models for modeling NMS is limited by the fact that many of these symptoms are at least partially independent of DA. For example, current research into the cognitive and behavioral impairments observed in PD suggests a role for the serotonin (5-HT), norepinephrine (NE), and acetylcholine (ACh) systems in addition to DA (Zgaljardic et al., 2004). Nevertheless, evidence has recently emerged regarding the ability of toxins directed at DAergic neurons to accurately replicate some of the NMS observed in PD.

6-OHDA

6-OHDA is toxic to catecholamine containing cells and needs to be stereotactically injected into target regions to ensure specificity of the lesion. If the toxin is injected into the substantia nigra (SN) or the median forebrain bundle, the DAergic neurons degenerate rapidly, producing a severe loss of striatal DA in only a few days (Faull and Laverly, 1969;

Zuch et al., 2000). In most studies desipramine was used jointly with 6-OHDA in order to preserve NE fibers (Waddington, 1980), and injections were often unilateral to avoid severe behavioral deficits that require special husbandry (Salin et al., 1996; Ungerstedt, 1971). Unilateral injections of 6-OHDA produce distinct motor impairments that include decreased rearing, akinesia, postural abnormalities and DA agonist-induced asymmetric rotating behaviors (Johnson et al., 1999; Schwarting and Huston, 1996). In contrast, when injected into the striatum (STR) the toxin produces a slower degradation of nigrostriatal neurons through a retrograde mechanism that occurs over a period of weeks (Przedborski et al., 1995). An advantage of this approach is that it may produce partial lesions that could enable the detection of NMS without the presence of severe motor impairment, a factor likely to confound results. In studies that focus on the NMS, investigators often used a partial, bilateral lesion which typically does not lead to overt motor dysfunction, although sensitive tests of motor behavior can reveal significant changes (Tillerson et al., 2002).

Multiple studies have used this bilateral administration of 6-OHDA into the STR in an attempt to model the neuropsychiatric symptoms of PD which include, but are not limited to, cognitive impairment, depression, and anxiety (Schrag, 2004). One of the most comprehensive experiments was completed by Tadaiesky et al. (2008). Rats underwent infusions of 6-OHDA (12 μ g) bilaterally into the dorsal STR. Analysis of behavioral and biochemical parameters was performed one week and three weeks after surgery. Results showed that after just one week, rats with 6-OHDA lesions have shown approximately a 40% decrease in the density of tyrosine hydroxylase (TH) staining in the STR and a 60% decrease in the SNpc, without significant changes in spontaneous locomotion. In terms of NMS, 6-OHDA-treated rats exhibited a decrease in sucrose consumption and an increase in immobility time in a forced swimming test after one week, suggestive of anhedonia and behavioral despair, respectively. In addition to this depression-like state, three weeks after surgery rats showed increased anxiety as determined by a decrease in the entry in open arms, but not total arm entries, during an elevated plus-maze test. Lastly, the rats took longer to find the platform in a cued water maze task and did not display social odor recognition, despite no impairment in general odor recognition. Both deficits indicate altered cognitive function. Biochemical analysis revealed lower levels of DA and its metabolites in the STR and pre-frontal cortex, but not the hippocampus, in rats with lesions. These animals also showed changes in the levels of 5-HT and NE in the STR. Overall this study indicates that some of the neuropsychiatric NMS of PD can be replicated in the 6-OHDA-induced rat model of parkinsonism and suggests the indirect involvement of multiple neurotransmitter systems.

Similar results published by other laboratories generally corroborate the findings from Tadaiesky and colleagues. Another group found that a bilateral injection of 6 μ g of 6-OHDA into the SNpc of rats led to the development of spatial memory deficits in the water maze test three weeks after surgery with no significant differences in locomotor behavior (open field test). Eight weeks after surgery, histology revealed a 90% loss of TH-immunoreactive (TH-ir) neurons in the SNpc and an 85% loss of DA in the STR of rats with lesions compared with control rats (Ferro et al., 2005). Santiago et al. (2010) used a bilateral injection of 6 μ g 6-OHDA into the SNpc and found that these rats displayed anhedonia (in the sucrose preference test) after one week, along with behavioral despair (in the forced swimming test) and no changes in locomotion after three weeks. This approach also resulted in approximately 60% loss of SNpc neurons and significant decreases in the levels of DA, 5-HT, and NE in the hippocampus. Overall, there is growing evidence that 6-OHDA can model some of the neuropsychiatric aspects of PD.

Some of the available literature reveals that the toxin model can also be used to mimic a few additional NMS observed in PD patients such as pain, circadian deficits, and GI dysfunction

(Djaldeiti et al., 2004; Edwards et al., 1991; Whitehead et al., 2008). In one experiment rats were injected unilaterally with 5 µg of 6-OHDA into the STR and examined for changes in nociceptive behavior. Results revealed a hyperalgesic response to chemical stimulation of the face, and mechanical and thermal stimulation of the hind paws over the course of three weeks, with a severe loss of TH-ir neurons in the SNpc in the lesioned rats (Chudler and Lu, 2008). A unique method was used by Gravotta et al. (2011) to analyze circadian rhythm alterations in the 6-OHDA exposed rat. An intracerebroventricular injection of 300 µg of the toxin was combined with a pre-surgery injection of desipramine to protect NE fibers (Breese and Traylor, 1971). Results show a toxin-induced disruption of wheel-running activity with a decrease in total running time and a disorganization of free-running patterns, supporting a role for DA in circadian rhythmicity (Gravotta et al., 2011). A recent study by Zhu et al. (2011) examined the effects of a unilateral, 12 µg injection of 6-OHDA into the SN on GI functioning. After four weeks, the lesioned rats exhibited a delay in stomach emptying, a decrease in colon motility, and roughly a 75% loss of neurons in the SNpc.

Taken together, these studies show that stereotaxic injections of 6-OHDA can simulate some of the NMS observed in PD and induce changes in neurotransmitters other than DA, however whether these changes are due to direct toxicity or an indirect consequence of DA loss is not always clear. Also, since the pathogenesis of NMS is not well known, it is difficult to interpret the roles of each altered neurotransmitter system in these models. Notably, most NMS do not correlate with the stage of motor deficits and in fact can actually precede the development of motor symptoms by even decades (Abbott et al., 2005, 2007; Gonera et al., 1997; Ross et al., 2006; Weintraub et al., 2008). Indeed, NMS develop before the severe, permanent loss of DA in the basal ganglia motor circuit and present an opportunity for earlier evaluation and treatment of PD (Gerlach et al., 2011). While 6-OHDA models have great value in studying the motor aspects of the disease and the efficacy of classical anti-parkinsonian drugs, analysis of the NMS may be limited by the extent of the cell loss induced by this catecholaminergic neurotoxin.

MPTP

MPTP has the specific advantage of reproducing clinical motor symptoms in non-human primates to enable the testing of potential PD therapies. Although there are obvious benefits to using this species to more accurately mimic the symptoms of PD, these experiments are time consuming and costly. A few studies have analyzed the MPTP-induced parkinsonism model in non-human primates for the presence of NMS. For this purpose, the toxin was typically administered at a low dose (0.01–0.175 mg/kg) over several weeks to avoid the development of rapid and severe motor problems that prevent the examination of the initial stages of the disease (Schneider and Kovelowski, 1990).

Similar to the studies using 6-OHDA, the effects of MPTP on cognition has been the most widely examined NMS to date. A study using adult *macaca fascicularis* monkeys that were exposed to low doses of MPTP for 24 weeks revealed cognitive deficits (impairment in object retrieval task) prior to the development of observable motor dysfunction (Schneider and Pope-Coleman, 1995). In addition, another group using Rhesus macaques (*macaca mulatta*) exposed to a chronic, low dose administration of the toxin reported no severe skeletal motor problems, but rather impairments in frontal lobe cognition (spatial delayed-response task) and oculomotor functioning (saccadic deficits) that coincided with a 75% loss of TH-ir neurons of the SNpc (Slovin et al., 1999). Remarkably, a longitudinal study of Rhesus macaques determined that ten years after receiving low doses of MPTP the animals continued to exhibit spatial deficits (spatial delayed-response task), however they displayed no obvious motor impairments except an occasional tremor of the hands (Fernandez-Ruiz et al., 1995). These studies suggest that a chronic method of MPTP administration to primates can produce a progressive phenotype in which NMS can appear before the development of

the clinical motor symptoms of PD, as in patients. This provides a large window to test the efficacy of drug treatments. For example, Decamp and Schneider (2004) first documented a lack of motor symptoms and the presence of deficits in attention and executive function (attention set shifting tasks, discrimination reversals, and sustained/focused attention tasks) in a low dose MPTP model in Rhesus macaques. They then used this primate model of parkinsonism to test the effects of L-DOPA, nicotine, and a nicotinic ACh receptor agonist on the cognitive dysfunction. Alone L-DOPA further impaired performance on the cognitive behavioral tasks, however this could be counteracted with co-administration of nicotine or a nicotinic receptor agonist (Decamp and Schneider, 2009). These results corroborate data showing that patients with mild PD that were medicated with DAergic drugs perform worse on certain cognitive tasks than their non-medicated counterparts (Cools et al., 2001; Swinson et al., 2000). Interestingly, a similar phenomenon was found in rats injected with MPTP bilaterally into the SNpc. Rats displayed an impairment of memory acquisition and retention processes (lower scores on two-way active avoidance task) that was worsened with L-DOPA treatments, yet improved with caffeine administration (Da Cunha et al., 2001; Gevaerd et al., 2001). It has been suggested that L-DOPA-induced increases in DA release in extrastriatal circuits can impair cognition in some PD patients while improving motor functioning (Kulisevsky, 2000), stressing the importance of DA function in multiple brain circuits (Cools et al., 2007).

Whereas the chronic MPTP model of parkinsonism in primates has been utilized extensively for determining DAergic-specific motor and cognitive symptoms of PD, more acute regimens have been used to assess other NMS in the primate model. Multiple injections of 0.5 mg/kg of MPTP in Rhesus macaques produced bradykinesia, rigidity and a 95% decrease in levels of DA and its metabolites in the STR approximately 90 days after treatment. A loss of rapid eye movement (REM) sleep and excessive daytime sleepiness appeared after the first injection, before the development of the motor deficits. Interestingly, three years after treatment a partial restoration of motor behavior coincided with a partial increase in REM sleep (Barraud et al., 2009). In support of these findings, a prior study using cynomolgous monkeys (*Macaca fascicularis*) and higher doses of MPTP (2–4 mg/kg) found significant decreases or the complete absence of REM sleep in addition to motor dysfunction (Almirall et al., 1999). It remains unknown if this dramatic change in REM sleep is related to the pre-symptomatic REM behavioral disorder (RBD) seen in PD patients.

Unfortunately, it does not seem that the MPTP model has, as of yet, been proven particularly useful to study other NMS. A study with Rhesus macaques revealed that acute or chronic exposure to MPTP was not able to produce the sympathetic denervation of the heart observed in PD patients (Goldstein et al., 2003). In addition, low doses of MPTP given through intravenous administration to Rhesus macaques that caused the development of bradykinesia and rigidity did not induce GI dysfunction despite a significant decrease of TH-ir neurons in the enteric nervous system (Chaumette et al., 2009).

The use of MPTP in non-human primates has expanded our knowledge, particularly of DA-mediated cognitive functions, but a variety of NMS have also been examined in models of MPTP-induced parkinsonism in mice. Multiple intraperitoneal injections of MPTP in mice can produce the classical histological feature leading to parkinsonism, i.e. the death of nigrostriatal DAergic neurons. Vuckovic et al. (2008) reported results for a wide range of NMS in this model, with a focus on identifying the role of multiple neurotransmitters. Mice were given 20 mg/kg of the toxin for a total of four injections and were then observed for deficits in a variety of tasks. By 30 days after MPTP injections, mice developed deficits in associative memory (social transmission of food preference) and conditioned fear (auditory fear conditioning task). However, there were no signs of anxiety (light/dark preference; hole-board) or depression (sucrose preference and tail suspension). In addition to a 65% loss

of TH-ir neurons in the SNpc, these animals also showed a significant decrease in the levels in DA and 5-HT in the STR, frontal cortex, and amygdala. Another group found that a similar injection series in mice produced hyper-algesia, as demonstrated by a reduced latency to a tail flick and constant temperature hot plate test, and decreased DA in the STR and increased 5-HT in the forebrain (Rosland et al., 1992). While it is known that patients with PD develop central serotonergic dysfunction, and that this may appear before the presence of motor symptoms, the temporal relationship between the neurochemical changes in DA, NE, and 5-HT and the development of NMS are still unclear (Kano et al., 2011).

An additional NMS study determined that mice given doses of 25 mg/kg of MPTP over five days immediately develop an overall increase in REM sleep during both light and dark phases. Histology showed a 30% decrease in DA neurons of the SN and little or no TH-ir in the STR (Monaca et al., 2004). Importantly, a follow-up study by this group revealed that despite a stable loss of the nigrostriatal pathway for up to 60 days, REM sleep was restored within 40 days of the initial MPTP exposure (Laloux et al., 2008). These data bring into question the ability of MPTP in rodents to mimic the chronic sleep alterations observed in PD (Lima et al., 2007). A similar transient appearance of a NMS in an MPTP mouse model was reported by Anderson et al. (2007). In this study, MPTP exposure caused a 57% decrease of TH-ir in the SNpc, a 52% decrease in the STR and a 40% reduction in the enteric nervous system 10 days after the injections. However the behavioral phenotype of GI dysfunction was limited to a temporary increase in colonic motility (the opposite of what is observed in patients) and there were no changes in gastric emptying.

Olfactory deficits are yet another NMS difficult to replicate in the MPTP mouse model. It was shown a number of years ago that unlike PD patients, individuals with MPTP-induced parkinsonism (usually due to parenteral self-administration) did not show olfactory dysfunction (Doty et al., 1992). In contrast, intranasal administration of MPTP in mice produces deficits in olfaction (familiar odor recognition) after five days of exposure and changes in cognition (social recognition and water maze) after 15 days. This mode of administration also decreased DA in the prefrontal cortex, NE in the hippocampus, and both transmitters in the olfactory bulb (OB) and STR (Prediger et al., 2010). A similar behavioral phenotype was also observed after intranasal administration of MPTP in the rat (Prediger et al., 2006). Mice exposed to MPTP using an intraperitoneal route of administration (20 mg/kg for four injections) displayed a specific decrease in NE in the OB, with no significant changes to DA (Dluzen, 1992). While these studies may not mimic the early alterations to the olfactory system seen in sporadic PD, they provide a different approach to study the role of NE in MPTP toxicity and as a target for therapeutic manipulation (Rommelfanger et al., 2004). NE may also play a critical role in the autonomic NMS observed in PD patients, including orthostatic hypertension and sympathetic denervation. Both PD patients and mice exposed to MPTP show a reduction in accumulation of cardiac ^{123}I -metaiodobenzylguanidine, an analog of NE that is used as an index of sympathetic function (Takatsu et al., 2000).

Overall, the use of MPTP in the mouse can provide a unique tool for the study of the circuitry involved in some NMS, but there are significant aspects of the model that can limit this approach, particularly the transient nature of the symptoms, which presents a challenge for testing neuroprotective treatments. The primate model of MPTP-induced parkinsonism has been extremely valuable in testing efficacious DAergic therapies (Bibbani et al., 2005). However, the toxin does not accurately replicate the global and progressive degeneration seen in the disease. As briefly described above, these models have the ability to mimic DAergic cell loss and even some non-motor characteristics of PD. However, maybe just as important are the symptoms that the toxin cannot replicate. For example, multiple studies report a lack of anxiety after MPTP exposure, suggestive of extranigral involvement in this

frequent symptom of PD (van Vliet et al., 2006; Vuckovic et al., 2008). In this regard, the specificity of MPTP can be used to help elucidate the role of DA in the development of some NMS.

Rotenone and other environmental toxins

There is increasing evidence that contact with environmental toxicants, such as pesticides, can be associated with an increased risk of PD, potentially through gene-environment interactions (Brown et al., 2006; Tanner et al., 2011; Wang et al., 2011). Some studies in rodents have begun to examine the ability of compounds, such as rotenone, paraquat, and cycad, to mimic various aspects of the disease, although variability in phenotypes has been a significant hurdle to overcome. Rotenone administration in rats has been shown to lead to lesions of the nigrostriatal pathway and aSyn accumulation (Cannon et al., 2009), yet the lack of specificity of the toxin and the variability of its effects in earlier studies have limited its use for evaluating neuroprotective strategies (Fleming et al., 2004b; Zhu et al., 2004). Nevertheless, multiple NMS have been successfully examined in this model. Rats that received a subcutaneous infusion of rotenone over 30 days showed a decrease in locomotor activity and loss of neurons of the SNpc, accompanied with an increase in slow-wave sleep (SWS) and REM sleep during the animal's active phase and decreased SWS during the rest phase. This excessive sleepiness was eliminated through intracerebroventricular administration of an interleukin-1-beta receptor antagonist, but not DA or a gamma-aminobutyric acid (GABA) antagonist (Yi et al., 2007). These results are of particular interest in view of the growing body of literature that suggests a role for cytokines in NMS development (Arman et al., 2010; Menza et al., 2010). In terms of neuropsychiatric symptoms, rats that underwent bilateral infusion of rotenone into the SN displayed depressive behavior in a forced swim and sucrose preference task, as well as changes to hippocampal levels of 5-HT and NE metabolites (Santiago et al., 2010). Chronic rotenone administration altered cognition in rats as shown by an increase in transfer latency in an elevated plus maze (time to enter closed arm) that could be improved with an oral treatment of lycopene, a powerful antioxidant (Kaur et al., 2011). Lastly, two groups have recently presented evidence that rotenone can induce GI dysfunction as determined by aSyn aggregation in the enteric nervous system, loss of myenteric neurons of the small intestine (Drolet et al., 2009), a delay in gastric emptying, and impaired functioning of inhibitory neurons in the enteric nervous system (Greene et al., 2009). Overall, despite the high variability of rotenone effects, the progressive and non-DAergic specificity of the toxin expands opportunities for the study of NMS of PD. However, it remains unproven that the mechanism of NMS observed in rotenone-treated animals is the same as those presented by patients.

The use of other environmental toxin-induced models to study NMS of PD is still in the beginning stages. The herbicide paraquat (1,1'-dimethyl-4,4'-bipyridinium) has been shown to cause highly reproducible degeneration of DAergic neurons and accumulation of aSyn in mice (Fernagut et al., 2007; Manning-Bog et al., 2002; McCormack et al., 2002), but few studies have examined NMS in this model; an exception is one study showing increased anxiety in paraquat treated mice (Litteljohn et al., 2008). Another provocative toxicant-induced model of parkinsonism utilizes the seeds of the *cycas micronesica* (cycad) plant that has been linked to the development of amyotrophic lateral sclerosis/parkinsonism dementia complex. Mice fed washed cycad flour display a progressive phenotype with some PD-like symptoms including degeneration of DAergic neurons of the SNpc and cognitive deficits as shown by increased latency to find the platform in a water-maze task and an increased number of errors in a radial-arm maze (Wilson et al., 2002). Cycad-fed rats show a progressive loss of DAergic neurons of the SNpc, aSyn accumulation in multiple brain regions, and early alterations of sleep/wake activity characterized by an increase in SWS and

REM sleep during the active phase (McDowell et al., 2010; Shen et al., 2010). This model provides a different approach with which to study the progressive neurodegeneration observed in PD, also enabling for the stable detection of NMS.

The non-motor features of genetic models of parkinsonism

Research into the pathogenesis of PD is expanding as evidence accumulates that protein and/or cellular mechanisms affected by gene mutations linked to familial forms of PD are also involved in sporadic forms of the disease (Shulman et al., 2011). One of the most pivotal findings occurred in the 1990s when the protein α Syn, which when mutated or overexpressed causes familial PD, was found to aggregate into Lewy bodies in both familial and sporadic cases of PD (Kruger et al., 1998; Polymeropoulos et al., 1997; Spillantini et al., 1998). Other gene mutations, such as those found in PINK1 (*PARK6*), DJ-1 (*PARK7*) and parkin (*PARK2*), cause early-onset familial PD (Bonifati et al., 2003; Lucking et al., 2000; Valente et al., 2004). These discoveries have led to a large amount of research over the past two decades including the development of numerous genetic animal models (Magen and Chesselet, 2010).

In addition to disease-causing mutations, genetic risk factors for PD have also provided a rationale for developing models with which to study the disease. For example, reduced vesicular monoamine transporter (VMAT2) activity is reduced in the brains of PD patients (Miller et al., 1999), and a gain of function VMAT2 haplotype is protective against PD in humans (Glatt et al., 2006). Also, the transcription factor PITX3 is important for the differentiation and survival of midbrain DAergic neurons during development, and polymorphisms in this gene have been linked to early-onset and sporadic cases of PD (Bergman et al., 2010; Fuchs et al., 2009; Le et al., 2011; Nunes et al., 2003). Unlike the original and severe toxin-induced parkinsonian phenotype, some of the aforementioned genetic manipulations in mice can induce a mild and progressive involvement of DAergic system dysfunction and motor problems (Magen and Chesselet, 2010). Initial work suggests that genetic models could also be well-suited to study NMS of the disease.

Wild-type α Syn models

Mice that overexpress wild-type (WT) α Syn, under the Thy1 promoter (Thy1- α Syn), has been extensively examined for the presence of NMS (Magen and Chesselet, 2010). These animals exhibit a progressive development of sensorimotor deficits beginning as early as two months of age, and α Syn accumulation in multiple brain regions such as the SN, however not in the spinal cord (Fleming et al., 2004a; Rockenstein et al., 2002). Some of these early behavioral deficits were not responsive to treatment with DAergic agonists, which is not surprising because at this time point the mice do not exhibit any significant loss of DA terminals in the STR or DAergic cells in the SN (Fleming et al., 2006). In fact, Thy1- α Syn mice display elevated tonic DA levels in the STR at six months of age that progresses to a significant decrease in DA and TH content by 14 months of age (Lam et al., 2011). By three months of age Thy1- α Syn mice displayed olfactory deficits as shown by an increased latency to find a hidden odorant, and decreased performance on non-self odor recognition and habituation/dishabituation tasks (Fleming et al., 2008b). Also at this early age, Thy1- α Syn mice exhibit progressive alterations in circadian rhythms and signs of autonomic dysfunction evidenced by lower night-time activity with a greater fragmentation in wheel-running, and increased heart rate variability, respectively (Fleming et al., 2009; Kudo et al., 2011). Cognitive changes evident from fewer alternations in a Y-maze, decreased novel object recognition, and deficits in operant reversal learning are also evident in the Thy1- α Syn mice beginning around four to six months of age (Fleming et al., 2008a; Magen and Chesselet, 2010). These mice also show apparent decreases in classical tests of anxiety such as the elevated plus maze, intruder test, and light-dark box (Mulligan et al., 2008) that are

likely related to their early hyperactivity (Lam et al., 2011). Indeed, they exhibit increased anxiety in fear conditioning tests, without changes in pain threshold (Torres et al., 2010). Another study revealed GI dysfunction exhibited by abnormal colonic motility in 11-month-old Thy1-aSyn mice (Wang et al., 2008). Overall, the broad expression of the transgene in this model of parkinsonism has enabled the successful detection of an extensive set of NMS.

Mice overexpressing WT aSyn under regulation of the platelet-derived growth factor-beta (PDGF- β) promoter display a progressive increase in aSyn aggregation in multiple brain regions, a loss of DAergic terminals in the STR and mild changes in motor activity as shown by a decreased latency to fall on a rotarod. By six months of age these transgenic mice also exhibited deficits in cognition shown by an increased time to find the platform in the water maze task (Masliah et al., 2011). Using a tetracycline-regulated tet-off system (tTA), Nuber et al. (2008) created a conditional mouse model for the overexpression of WT aSyn under the calcium/calmodulin-dependent protein kinase II α (CaM) promoter. These mice displayed a progressive motor decline after 7 months (rotarod), impaired memory after 12 months (water maze), aSyn accumulation in the SN, hippocampus and OB, and a loss of TH-ir cells in the SN (Nuber et al., 2008).

Mutant aSyn models

Multiple mouse models expressing mutated forms of aSyn have been developed in hopes of accelerating the pathological process and creating a more complete parkinsonian phenotype. Here again the most extensively studied NMS are cognitive deficits. A transgenic mouse model expressing the A30P variant of aSyn under control of the murine Thy1 promoter revealed aSyn inclusions in several brain regions including the amygdala and hippocampus, motor impairment after 17 months of age, and at 12 months of age, cognitive deficits in the Morris water maze and auditory fear conditioning tasks (Freichel et al., 2007).

Overexpression of an Y39C form of aSyn, a mutation not found in humans but that increases aggregation, under the mouse Thy1 promoter induced progressive aSyn accumulation, a decrease in motor functioning on the rotarod, and cognitive deficits in the Morris water maze (Zhou et al., 2008). Mice overexpressing the A30P variant of aSyn under the mouse prion promoter showed decreases in NE levels but not DA levels in the STR and OB, and reduced anxiety-like behavior in the elevated plus maze (George et al., 2008; Sotiriou et al., 2010).

Cognitive deficits dominate the clinical features of diffuse Lewy body disease (DLB), a synucleopathy related to PD, but with extensive and early Lewy body pathology in the cerebral cortex. Therefore, investigators have attempted to mimic the pathological features of DLB to better reproduce the cognitive deficits associated both with DLB and advances stages of PD. By using a tet-off system and the CaMKII α promoter, Lim and colleagues developed a transgenic mouse expressing a mutant (A53T) aSyn (tTA/A53Ta-syn) in the fore-brain. These mice displayed aSyn pathology resembling the distribution observed in DLB, with accumulation of aSyn in the hippocampus and other limbic areas that correlated with impairments in contextual fear memory; furthermore, suppression of the transgene attenuated these deficits (Lim et al., 2011).

Other NMS have been less extensively studied in mice expressing mutated aSyn, however, Kuo et al. (2010) have uncovered GI deficits in a transgenic model that utilizes the A53T variant of aSyn. Briefly, cross-breeding of a transgenic mouse expressing a P1 artificial chromosome containing the full length SNCA gene with the A53T mutation with a *Snca*^{-/-} mouse, enabled creation of a transgenic cohort of mice expressing only the mutant human protein. These animals displayed decreases in motor activity (open field test) and at as early as three months of age show GI dysfunction reflected by reduced fecal mass and decreased colonic motility. However at 18 months of age, these mice do not exhibit changes in cardiac

autonomic abnormalities, olfactory dysfunction, nor loss of neurons in the SN or DAergic terminals in the STR (Kuo et al., 2010). While this transgenic model is very informative as to the early changes in the enteric nervous system, they lack evidence of nigrostriatal involvement, a key part of the parkinsonian phenotype.

Other genetic models

Two models of early-onset, familial forms of PD that have shown non-motor behavior include DJ-1 knockout and parkin knockout mice. Goldberg et al. (2005) reported that DJ-1 knockout mice had normal numbers of DA neurons in the SN, but displayed a significant decrease of DA in the STR. However, in an independent study, DJ-1 knockout mice displayed some progressive changes in motor behavior with no significant changes to the nigrostriatal DAergic system (Chandran et al., 2008). Interestingly, DJ1^{-/-} mice between 13 and 14 months of age show cognitive deficits characterized by reduced performance in an object recognition task (Pham et al., 2010). Mice that lack exon 3 in the parkin gene do not demonstrate a loss of DAergic neurons but show signs of altered synaptic transmission in the nigrostriatal circuit (Goldberg et al., 2003). Another line of parkin^{-/-} mice displays increased anxiety, as shown in open field and light/dark preference tests, and cognitive impairment exhibited as spatial deficits in the Morris water maze (Zhu et al., 2007). It is likely that these models, which utilize recessive gene mutations, may need additional stresses to the system in order to induce a more classical neurodegeneration. For example, DJ-1 deficient mice show increased sensitivity to MPTP or paraquat exposure (Kim et al., 2005; Yang et al., 2007), reinforcing the importance of the role of gene-environment interactions on PD development. In addition, a conditional knock out of the protein after birth may bypass compensatory mechanisms taking place during development and expose the full effect of the mutation on DAergic neurons, as shown for conditional parkin mutations (Shin et al., 2011). These new models may provide additional opportunities to replicate and study NMS of PD in the near future.

Genetic risk factor models

Accumulation of cytosolic DA can increase levels of reactive oxygen species, a key mediator of PD pathology (Jenner, 2003; Rabinovic et al., 2000). VMAT2 packages several monoamines into synaptic vesicles and its ability to remove DA from the cytosol may be neuroprotective (Guillot and Miller, 2009). In turn, diminished expression or function of VMAT2 could reduce DAergic neuron survival (Lawal et al., 2010). VMAT2-deficient (VMAT2 LO) mice, that display a 95% reduction in VMAT2 gene expression, exhibit a decrease in the levels of DA, NE, and 5-HT. In addition, they show a progressive degeneration of the nigrostriatal pathway, motor deficits, and aSyn accumulation (Caudle et al., 2007). A follow-up study of these mice revealed the presence of olfactory deficits, GI dysfunction, sleep disruption, increased anxiety and depression (Taylor et al., 2009). More specifically, the VMAT2 LO mouse exhibits a chronic deficit in nonsocial olfactory acuity (odor discrimination task) by five months of age. Between 2–12 months of age the mice display some delays in gastric emptying. A transient shortening in sleep latency peaked at 4–6 months of age, and disappeared by 24 months of age. Lastly, these mice show early symptoms of anxiety (6 months) and later signs of depression (15 months), as shown by an increased time in the closed arms of an elevated plus maze and time spent immobile in a forced-swim test. Together the data suggest that this model shows some of the NMS of PD as a result of a chronic reduction in multiple neurotransmitters that have also been implicated in the progression of the disease.

The aphakia mouse, which is deficient in the transcription factor PITX3, provides another model of a PD risk factor. These mice display a severe (over 90%) loss of DAergic neurons of the SNpc, with relative preservation of neighboring brain regions such as the VTA

(Hwang et al., 2003). As a result of the nigrostriatal DA loss, they exhibit parkinsonian motor deficits that are reversed by L-DOPA (Hwang et al., 2005). Not unexpectedly, these mice display alterations in STR-dependent cognitive behaviors (Ardayfio et al., 2008; Hwang et al., 2005). This model further supports a role for DAergic cell loss and nigrostriatal dysfunction in cognitive behaviors, as previously suggested based on observations made in toxicant models of parkinsonism.

A final risk factor model of PD that shows NMS involves the modification of the class IV alcohol dehydrogenase (ADH4), an enzyme that neutralizes potentially toxic aldehydes produced from lipid peroxidation. It has been shown that protein adducts from this pathway can be elevated in the SN of PD patients (Yoritaka et al., 1996). ADH4 knockout mice at least 12 months of age do not display significant differences in spontaneous locomotor activity, but rather an impairment of olfaction exhibited by an increase in the time required to complete a hole-poke task. Analysis of DA, its metabolites, NE, and 5-HT in the OB, STR, SN, and cortex revealed only a modest increase of DOPAC in the OB, and DOPAC and DA in the SN (Belin et al., 2011). Additional studies are necessary to determine the utility of risk factors like ADH4 in successfully modeling the cardinal features of PD.

Although most of the genetically engineered models of PD do not display all of the classical motor deficits and severe loss of the nigrostriatal circuit, many display alterations in DAergic physiology that may represent earlier stages of disease progression and could help explain the etiology behind some of the NMS. The progressive nature of symptom development and broad range of NMS observed in the Thy1-aSyn mouse model enables a long window for therapeutic testing. In addition, risk factors such as VMAT2 have provided support for the idea that multiple neurotransmitters and brain regions are involved in disease progression. While the use of genetic models to study PD is relatively new, especially when compared to the toxin models previously discussed, they are beginning to offer multiple new ways for understanding the NMS of this debilitating disease.

Acknowledgments

Supported by PHS grant P50 NS38367 (UCLA, Morris K. Udall Parkinson Disease Research Center of Excellence), and PHS grant P01ES016732 (the UCLA Center for Gene Environment in Parkinson's Disease).

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Table 1

Preclinical PD model	Olfaction	Sleep/circadian rhythm	Gastrointestinal	Cardiovascular	Anxiety	Depression	Cognition	Noiception
6-OHDA	-----	X _R ¹	X _R ²	-----	X _R ³	X _R ^{3,4}	X _R ^{3,5}	X _R ⁶
MPTP	X _{R,M} ^{7,8}	X _{P,R,M} ⁹⁻¹³	X _M ¹⁴	X _M ¹⁵	-----	X _R ⁴	X _{P,R,M} ¹⁶⁻²²	X _M ²³
Rotenone	-----	X _R ²⁴	X _R ²⁵⁻²⁶	-----	-----	X _R ⁴	X _R ²⁷	-----
Paraquat	-----	-----	-----	-----	X _M ²⁸	-----	-----	-----
Cycad	-----	X _R ²⁹	-----	-----	-----	-----	X _M ³⁰	-----
Thy1-aSyn	X ³¹	X ³²	X ³³	X ³⁴	X ³⁵	X ³⁶	X ³⁷	-----
Other aSyn [*]	-----	-----	X _b ³⁸	-----	X _b ³⁹	-----	X _{c,f} ⁴⁰⁻⁴³	-----
DJ-1 KO	-----	-----	-----	-----	-----	-----	X ⁴⁴	-----
Parkin KO	-----	-----	-----	-----	X ⁴⁵	-----	X ⁴⁵	-----
VMAT LO	X ⁴⁶	X ⁴⁶	X ⁴⁶	-----	X ⁴⁶	X ⁴⁶	-----	-----
PTX3 KD	-----	-----	-----	-----	-----	-----	X ⁴⁷	-----
ADH4 KO	X ⁴⁸	-----	-----	-----	-----	-----	-----	-----

Note that species (R = rat; M = mouse; P = primate) is only indicated for toxin based models. All genetic models presented are in mice.

^{*} For "Other aSyn" models genetic constructs are characterized by a subscript letter. a=PAC-Tg(SNCA A53T)^{+/+}; *Sncg*^{-/-}; b=prion aSynA30P; c=PDGF-b aSyn; d=CaM-rTA aSyn; e=Thy1-aSynA30P; f=Thy1-aSyn Y39C.

References:

- 1 Gravotta et al., 2011;
- 2 Zhu et al., 2011;
- 3 Tadaiesky et al., 2008;
- 4 Santiago et al., 2010;
- 5 Ferro et al., 2005;
- 6 Chudler and Lu, 2008;
- 7 Prediger et al., 2006;
- 8 Prediger et al., 2010;

- ⁹ Almirall, et al., 1999;
- ¹⁰ Monaca et al., 2004;
- ¹¹ Lima et al., 2007;
- ¹² Laloux et al., 2008;
- ¹³ Barraud et al., 2009;
- ¹⁴ Anderson et al., 2007;
- ¹⁵ Takatsu et al., 2000;
- ¹⁶ Fernandez-Ruiz et al., 1995;
- ¹⁷ Schneider and Pope-Coleman, 1995;
- ¹⁸ Slovin et al., 1999;
- ¹⁹ Da Cunha et al., 2001;
- ²⁰ Gevaert et al., 2001;
- ²¹ Decamp and Schneider, 2009;
- ²² Vuckovi et al., 2008;
- ²³ Rosland et al., 1992;
- ²⁴ Yi et al., 2007;
- ²⁵ Drolet et al., 2009;
- ²⁶ Greene et al., 2009;
- ²⁷ Kaur et al., 2011;
- ²⁸ Litteljohn et al., 2008;
- ²⁹ McDowell et al., 2010;
- ³⁰ Wilson et al., 2002;
- ³¹ Fleming et al., 2008a, b;
- ³² Kudo et al., 2011;
- ³³ Wang et al., 2008;

- ³⁴ Fleming et al., 2009;
- ³⁵ Mulligan et al., 2008;
- ³⁶ Fleming, unpublished observations;
- ³⁷ Magen and Chesselet, 2010;
- ³⁸ Kuo et al., 2010;
- ³⁹ George et al., 2008;
- ⁴⁰ Masliah et al., 2011;
- ⁴¹ Nuber et al., 2008;
- ⁴² Freichel et al., 2007;
- ⁴³ Zhou et al., 2008 ;
- ⁴⁴ Pham et al., 2010;
- ⁴⁵ Zhu et al., 2007;
- ⁴⁶ Taylor et al., 2009;
- ⁴⁷ Ardayfio et al., 2008;
- ⁴⁸ Belin et al., 2011.