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The Noradrenergic System is a Major Component in Parkinson's Disease

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1. Introduction

1.1 Dopaminergic neuronal loss in Parkinson's disease

Parkinson's disease (PD) is a neurological disorder that affects approximately 2% of the elderly population, and as our population continues to age, the incidence will only increase (Singh et al., 2007). PD is commonly characterized by various motor deficits including tremor, rigidity and bradykinesia (Singh et al., 2007). The cause of these motor symptoms is the loss of dopaminergic neurons in the substantia nigra pars compacta (SN) and reduced dopamine (DA) levels in the striatum (Damier et al., 1999; Gibb, 1991; Gibb and Lee, 1991). However, the appearance of PD symptoms does not occur until 70-80% of the dopaminergic neurons are lost. In the progression of this disorder, the loss of dopaminergic neurons is not observed until Stage 3 (out of 6 Stages) of the disorder (Braak et al., 2003a, 2003b, 2006).

1.2 Noradrenergic neuronal loss in Parkinson's disease

Of course a great deal of research has focused on the dopaminergic system in PD because loss of neurons in the SN is responsible for PD symptoms; however, PD is represented by multiple systems failing. During the earlier stages of the disorder, non-motor preclinical symptoms are observed. These preclinical symptoms include hyposmia (Berendse et al., 2001, Ponsen et al., 2004), REM-sleep disorder (Boeve et al., 2003, Scheneck et al., 2003), depression (Leentjens et al., 2003; Mayeux et al., 1992; Slaughter et al., 2001) and autonomic dysfunction such as orthostatic hypotension (Mathias, 1998; Ziemssen & Reichmann, 2007). These preclinical symptoms are attributed to neuropathological changes in neurotransmitter systems other than the SN dopaminergic nervous system. One neurotransmitter system that may be responsible for these early non-motor symptoms is the noradrenergic nervous system (Goldstein et al., 2011; Itoi & Sugimoto, 2010; Lopez-Munoz & Alamo, 2009; Mathias, 1998; Osaka & Matsumura, 1994; Ziegler et al., 1977). The presence of these symptoms would indicate an alteration in the noradrenergic nervous system is occurring early in the progression of PD. Postmortem examination of PD tissue demonstrates a significant loss of noradrenergic neurons in the locus coeruleus (LC); this loss is equal to or greater than the neuronal loss observed in the SN (Bertrand et al., 1997; Cash et al., 1987; Chan-Palay & Asan, 1989; Hornykiewicz & Kish, 1987; Marien et al., 2004; McMillan et al., 2011; Patt & Gerhard,

1993; Zarow et al., 2003). The loss of LC noradrenergic neurons also precedes the loss of dopaminergic neurons in the progression of PD (Braak et al., 2003b, 2006), correlating to the time that preclinical noradrenergic non-motor symptoms appear.

2. Noradrenergic cell bodies

2.1 Anatomical

There are two major clusters of noradrenergic neurons in the central nervous system (CNS): the LC and the lateral tegmental neurons. In contrast to the significant loss of LC noradrenergic neurons in PD as indicated above, the lateral tegmental group does not appear to demonstrate much of a loss in PD (Saper et al., 1991). LC noradrenergic neurons send projections to forebrain regions via three different tracts: the central tegmental tract, the central gray dorsal longitudinal fasciculus tract, and the ventral tegmental-medial forebrain bundle. A fourth tract innervates the cerebellum, and a fifth tract innervates the spinal cord. The rostral portion of the LC innervates forebrain structures such as the hippocampus, whereas the caudal portion of the LC innervates hindbrain structures such as the cerebellum and spinal cord (Aston-Jones et al., 1995; Fallon & Loughlin, 1982; Loughin et al., 1982, 1986b). The degree of LC innervation to forebrain regions compared to the lateral tegmental neurons varies from region to region, but the hippocampus and cortex appear to receive sole innervation from the LC (Aston-Jones et al., 1995; Jones & Moore, 1977; Loughlin et al., 1986a, b; Mason & Fibiger, 1970; Moore & Bloom, 1979; Olsen & Fuxe, 1971; Ungerstedt, 1971; Waterhouse et al., 1983). Innervation from the LC to forebrain regions also appears to be ipsilateral for the majority of regions (Ader et al., 1980; Room et al., 1981). Since the LC contains more than half of all noradrenergic neurons in the CNS (Aston-Jones et al., 2000), a reduction in the number of these neurons could have major consequences on the activity of many forebrain regions.

2.2 Synthesis of norepinephrine

The major neurotransmitter localized to noradrenergic neurons is norepinephrine (NE). However, NE is not the only transmitter released from noradrenergic terminals. Noradrenergic neurons also co-localize and release several other neuropeptides such as galanin, enkepalin and neuropeptide Y. NE and DA share a common synthetic pathway. NE is synthesized by several enzymatic steps (Figure 1): tyrosine is converted to L-3, 4-dihydroxphenylalanine (L-DOPA) by tyrosine hydroxylase (TH); L-DOPA is converted to DA by aromatic amino acid decarboxylase (AADC), and then in noradrenergic neurons DA is converted to NE by dopamine β-hydroxylase (DBH). In adrenergic neurons, NE is then converted to epinephrine by phenylthanolamine-N-methyltransferase (PMNT). TH is considered the rate-limiting enzyme in the synthesis of NE and DA. However, there is evidence to indicate that DBH activity can affect NE levels in the CNS when DBH levels are altered genetically (Thomas et al., 1995, 1998; Bourdelat-Parks et al., 2005), with excessive stimulation of noradrenergic neurons (Scatton et al., 1984) or when DBH inhibitors such as disulfiram or nepicastat are administered (Goldstein, 1966; Musacchio et al., 1966; Bourdelat-Parks et al., 2005; Beliaev et al., 2006; Schroeder et al., 2010). DBH knockout mice lack the ability to convert DA to NE so the CNS levels of DA are elevated as compared to wild-type mice (Thomas et al., 1995, 1998). NE levels in the periphery and CNS can be restored in DBH knockout mice with the peripheral administration of L-3,4-dihydoxyphenylserine (DOPS). DOPS is converted to NE through AADC, in noradrenergic and non-noradrenergic neurons. TH knockout mice lack the ability to synthesize both DA and NE (Zhou & Palmiter, 1995).

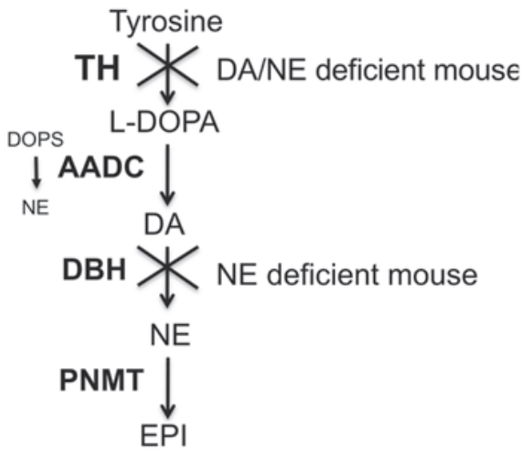

Fig. 1. Catecholamine biosynthesis and production of catecholamine knockout mice.

3. Consequence of LC neuronal loss in PD

3.1 Alterations in terminal noradrenergic markers

The loss of LC noradrenergic neurons in PD subjects should result in changes in NE levels at the various forebrain regions it innervates and the degree of loss should depend on the amount of LC innervation the region receives as compared to lateral tegmental groups. In PD subjects, there are reduced NE levels in the cortex, hypothalamus and cerebellum (Gasper et al., 1984, 1991; Kish et al., 1984; Shannak et al., 1994). TH- and DBH-immunoreactivity (IR) are also reduced in the cortex of PD subjects (Gasper et al., 1991). The reduction in neurotransmitter content and synthesizing enzymes in PD subjects can be attributed to the loss of noradrenergic innervation to these areas associated with the loss of LC noradrenergic neurons. The cortex, as indicated above, receives sole innervation from the LC, so changes in LC neuronal number would have a major impact in this region (Aston-Jones et al., 1995; Jones & Moore, 1977; Loughlin et al., 1986a, b; Mason & Fibiger, 1970; Moore & Bloom, 1979; Olsen & Fuxe, 1971; Ungerstedt, 1971; Waterhouse et al., 1983). Presently, the consequence of LC noradrenergic neuronal loss in PD on NE tissue content in the dopaminergic SN region is unknown.

3.2 Alterations in noradrenergic markers in LC

In contrast to terminal NE content in forebrain regions, NE levels in the LC of PD subjects does not appear to be different from controls (Cash et al., 1987). Examining different noradrenergic markers in the surviving LC neurons in PD subjects indicates the noradrenergic neurons are not compensating for the loss of surrounding neurons or terminal NE. The number of TH and DBH mRNA positively labeled neurons in the LC of PD subjects are significantly reduced as compared to age-matched control subjects (Szot, 2000, 2006; McMillan et al., 2011) and corresponds to the documented loss of noradrenergic neurons by other laboratories (Bertrand et al., 1997; Cash et al., 1987; Chan-Palay & Asan, 1989; Hornykiewicz & Kish, 1987; Marien et al., 2004; McMillan et al., 2011; Patt & Gerhard, 1993; Zarow et al., 2003). The degree of LC noradrenergic neuronal loss determined by TH and DBH mRNA expression in PD subjects is verified by counting the number of LC TH-IR positive labeled neurons (McMillan et al., 2011). TH mRNA expression/neuron of the

surviving LC noradrenergic neurons in PD subjects did not differ from TH mRNA expression/neuron in age-matched control subjects, indicating a lack of compensation of the surviving LC neurons (McMillan et al., 2011). Another marker of noradrenergic neurons, NE transporter (NET), was measured in the LC of age-matched and PD subjects. NET's function is to remove released NE from the synapse. Therefore, NETs are localized only to noradrenergic cell bodies, dendrites (peri-LC dendritic zone), and axon terminals of noradrenergic neurons. NET binding over cell body region and peri-LC dendritic zone in PD subjects is significantly reduced compared to age-matched control subjects and the loss of NET binding over the cell body region corresponds to the number of LC noradrenergic neurons in the LC (McMillan et al., 2011). The loss of NET binding in the peri-LC dendritic zone in PD subjects indicates the surviving LC neurons are not compensating for neuronal loss by increasing dendritic innervation. The loss of dendritic innervation in PD subjects, as determined by NET binding, is supported by reduced dendritic TH-IR labeling in the LC region of PD subjects as compared to age-matched controls (McMillan et al., 2011). However, the surviving LC neurons in PD subjects do demonstrate compensation in the expression of DBH mRNA (McMillan et al., 2011). The increased DBH mRNA expression/neuron in the surviving LC neurons of PD subjects may not be a response to neuronal loss because DBH mRNA expression/neuron is not altered in another neurodegenerative disorder with a significant loss of LC noradrenergic neurons (see below). Therefore, the increase in DBH mRNA expression/neuron observed in the surviving LC neurons in PD subjects may be a response to some other factor particular to PD, although it is unclear what that factor might be. The consequence of increased DBH mRNA expression of surviving LC neurons on NE levels in PD subjects is also unclear. Studies measuring cerebral spinal fluid (CSF) NE levels in PD subjects are variable. CSF NE levels and metabolites vary from reduced to no difference in postmortem and alive PD subjects (withdrawn from L-DOPA treatment) as compared to control subjects (Chia et al., 1993, 1995; Mann et al., 1983; Scatton et al., 1986; Turkka et al., 1987). As indicated above, NE tissue content is reduced, but LC concentration is similar to control subjects. These data suggest that NE levels and function may be reduced in PD, similar to DA levels and function.

3.3 Effect of L-DOPA treatment on noradrenergic system

The "standard gold" treatment for PD is L-DOPA. Administration of L-DOPA alleviates the symptoms associated with the loss of dopaminergic neurons (Cotzias et al., 1969); however, L-DOPA does not necessarily alleviate the non-motor symptoms associated with the loss of noradrenergic neurons (Sethi, 2008). Chronic administration of L-DOPA to PD subjects significantly elevates CSF levels of L-DOPA, DA and the DA metabolite dihydroxyphenylacetic acid (DOPAC) from age-matched control subjects (Figure 2A, B and C). There is a positive correlation of CSF DA levels to CSF L-DOPA levels. CSF NE levels in PD subjects on chronic L- DOPA treatment are not statistically different from age-matched controls (Figure 2B), but the NE metabolite 3,4-dihydroxyphenylglycol (DHPG) is significantly elevated in PD patients on chronic L-DOPA (Figure 2C). It is unclear why NE levels do not correlate to CSF L-DOPA levels in PD subjects like DA. A possible reason for the discrepancy in NE and DA levels in PD subjects on chronic L-DOPA therapy may be because administered L-DOPA is decarboxylated to DA in striatal neurons (as compared to DA from SN terminals) and serotonergic neurons, not in the few remaining dopaminergic

neurons (Huot & Parent, 2007; Yamada et al., 2007). Orthostatic hypotension, which is attributed to reduced CNS NE function, is relieved only with the administration of DOPS (Goldstein et al., 2011). DOPS is also used to normalize CNS levels of NE in the DBH knockout mouse that lacks the synthetic enzyme DBH that converts DA to NE (Figure 1) (Thomas et al., 1998). So these data would suggest that NE function in untreated PD and possibly treated subjects is reduced.

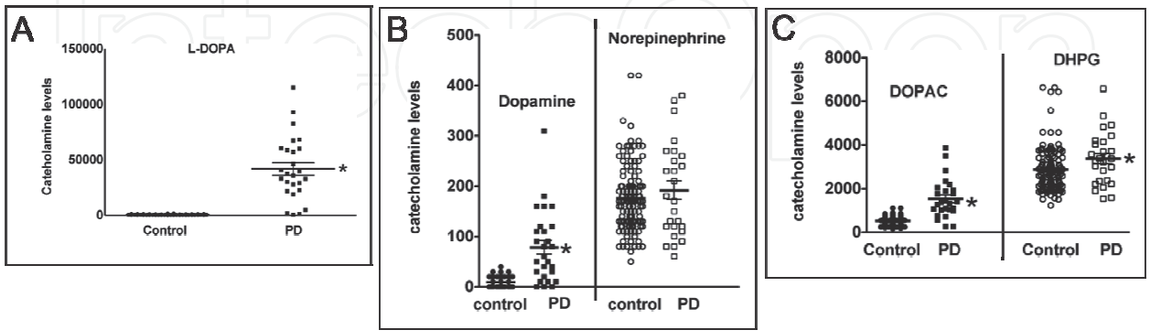

Fig. 2. CSF catecholamine levels in PD subjects on chronic L-DOPA treatment and age-matched control subjects. CSF spinal fluid was taken at the same time of day, approximately 4 hours after administration of L-DOPA. A) L-DOPA level, B) DA and NE levels and C) DOPAC and DHPG CSF levels in control and PD subjects on L-DOPA treatment. Catecholamine levels were extracted by alumina extraction and analyzed by high performance liquid chromatography (HPLC) as previously described (Szot et al., 2010). Each point represents a single individual catecholamine value for control and PD subjects, with average and standard error means (SEM) illustrated in bars for each catecholamine analyzed. * Indicates significant difference between control and PD subjects.

4. Comparison of the consequence of LC neuronal loss between PD and Alzheimer's disease (AD)

4.1 Alterations in terminal noradrenergic markers

Alzheimer's disease (AD), another neurodegenerative disorder, also exhibits significant LC noradrenergic neuronal loss (Bondareff et al., 1982; Chan-Palay & Asan, 1989; German et al., 1992; Mann et al., 1980; Marcyniuk et al., 1986; Szot et al., 2000, 2006; Tomlinson et al., 1981). However, unlike PD, in AD subjects the surviving LC noradrenergic neurons appear to be compensating for the loss. The content of NE in terminal regions of postmortem AD subjects is reduced, but the reduction does not correspond to the degree of neuronal loss (Adolfsson et al., 1979; Hoogendijk et al., 1999; Mann et al., 1981; Palmer et al., 1987; Reinikainen et al., 1988; Toghi et al., 1992; Tomlinson et al., 1981). Similar results were observed for IR of NE-synthesizing enzymes in the forebrain of postmortem AD subjects (Cross et al., 1981; Palmer et al., 1987; Perry et al., 1981; Russo-Neustadt et al., 1998). These data indicate that there is a reduction in NE function in forebrain regions of AD subjects, but it doesn't correlate to the degree of LC neuronal loss even in a region like the cortex which receives all of its innervation from the LC (Aston-Jones et al., 1995; Jones & Moore, 1977; Loughlin et al., 1986a, b; Mason & Fibiger, 1970; Moore & Bloom, 1979; Olsen & Fuxe, 1971; Ungerstedt, 1971; Waterhouse et al., 1983). These data suggest the surviving LC noradrenergic neurons in AD may be compensating for the lost neurons.

4.2 Alterations in noradrenergic markers in LC

To determine if the surviving LC noradrenergic neurons in AD subjects are demonstrating compensatory changes, several noradrenergic markers, similar to the markers used on the LC tissue of PD subjects, were assessed in the LC of subjects with AD. Work from my laboratory showed that the surviving noradrenergic neurons in the LC of AD and a related dementing disorder, dementia with Lewy body (DLB), showed compensatory changes. In subjects with dementia, the number of TH, DBH and NET mRNA positively labeled neurons in the LC are significantly reduced as compared to age-matched control subjects (Szot et al., 2000, 2006) and the degree of this LC neuronal loss corresponds to documented loss of noradrenergic neurons in AD by other laboratories (Bondareff et al., 1982; Chan-Palay & Asan, 1989; German et al., 1992; Mann et al., 1980; Marcyniuk et al., 1986; Tomlinson et al., 1981). The degree of LC noradrenergic neuronal loss determined by TH mRNA expression in AD subjects is verified by counting the number of TH-IR positive labeled neurons (McMillan et al., 2011).

	PD	AD
Neuronal Number	↓	↓
TH mRNA/neuron	—	↑
DBH mRNA/neuron	↑	—
NET cell body binding	↓	↓
NET peri-LC binding	↓	—
TH-IR surrounding LC	↓	—

Table 1. Changes in noradrenergic markers in the LC of PD subjects and subjects with dementia as compared to appropriate control groups.

However, in AD, the surviving LC noradrenergic neurons exhibit increased TH mRNA expression/neuron as compared to age-matched control subjects (Szot et al., 2000, 2006), suggesting compensation. NET binding over cell body region in the LC of AD subjects is significantly reduced as compared to age-matched control subjects, and the loss of NET binding over the cell body region corresponds to the number of LC noradrenergic neurons in the LC (Szot et al., 2006). However, NET binding sites over the peri-LC dendritic zone in AD subjects is not significantly different from age-matched control subjects, despite the reduction in LC noradrenergic neurons positively labeled for NET mRNA (Szot et al., 2000, 2006). The normal amount of NET binding in the peri-LC dendritic zone of AD subjects indicates dendritic sprouting of the surviving LC neurons. TH-IR labeling in dendritic region of AD supports the notion of enhanced dendritic innervation around LC noradrenergic neurons in AD subjects observed with NET binding (McMillan et al., 2011), again indicating compensation of the surviving LC neurons in AD. In addition to the sprouting in the LC, the surviving LC neurons in AD exhibit axonal sprouting into the hippocampus and prefrontal cortex (Szot et al., 2006, 2007). The difference in the response of the surviving LC noradrenergic neurons in PD and AD is observed even concerning DBH mRNA expression/neuron. In PD, DBH mRNA expression/neuron is elevated (as

indicated above), but in subjects with dementia where TH mRNA expression/neuron is elevated, DBH mRNA expression/neuron is not different from controls (McMillan et al., 2011). This suggests that the loss of LC noradrenergic neurons does not necessarily result in increased DBH mRNA expression/neuron. Compensation of the LC noradrenergic nervous system in AD subjects is also observed in CSF NE levels, where CSF NE levels are similar to or elevated to age-matched control subjects (Elrod et al., 1997; Gottfries et al., 1983; Mann et al., 1981; Raskind et al., 1984; Toghi et al., 1992).

4.3 Summary

It appears then the response of surviving LC noradrenergic neurons in AD, in regards to the noradrenergic markers measured, is completely different from the response of surviving LC noradrenergic neurons in PD (Table 1). These noradrenergic markers in AD suggest that noradrenergic function in AD subjects may not be reduced and may even exceed function in normal subjects, while in PD subject's noradrenergic function is reduced. This hypothesis is supported clinically. Orthostatic hypotension, a common non-motor symptom observed in PD due to reduced noradrenergic function, is not observed in AD subjects despite a similar degree of LC noradrenergic neuronal loss. A progression of noradrenergic function can be drawn between these two neurodegenerative disorders; at one of the spectrum PD represents the loss of LC noradrenergic neurons with reduced noradrenergic function, while AD represents the other end of the spectrum with the loss of LC noradrenergic neurons but enhanced noradrenergic function.

5. LC innervation of dopaminergic regions

As indicated above, LC noradrenergic neurons are reduced early in the progression of PD (Braak et al., 2003b, 2006). However, for the noradrenergic system to be involved in the progression of PD, LC noradrenergic neurons need to innervate the regions involved in the symptoms of PD (i.e., striatum and SN). There is evidence to indicate that the LC noradrenergic nervous system can modulate dopaminergic activity at the level of the striatum and the SN as well as the ventral tegmental area (VTA) at the anatomical, electrophysiological, neurochemical, and behavioral levels.

5.1 LC innervation to striatum

LC noradrenergic neurons have direct projections to the striatum, though evidence indicates this innervation may be sparse (Aston-Jones et al., 1995; Jones & Moore, 1977; Jones & Yang, 1985; Mason & Fibiger, 1979; Swanson & Hartman, 1975). When measured, NE concentration in the striatum is low (especially compared to DA), while NET binding (a marker of noradrenergic terminals) is not detectable (Szot, Personal communication; Koob et al., 1975; Nomura et al., 1976). However, the striatum does contain a dense amount of beta-adrenergic receptors (β-AR) (Byland & Snyder, 1976; Dolphin et al., 1979; Rainbow et al., 1984; Strazielle et al., 1999), as well as alpha2-AR (α_2-AR) (Szot, Personal communication; Boyajian et al., 1987; Hudson et al., 1992; Nicholas et al., 1992; Scheinin et al., 1994; Strazielle et al., 1999; Zeng and Lynch, 1991) and alpha1-AR (α_1-AR) (Szot, Personal communication; Rommelfanger et al., 2009; Strazielle et al., 1999) binding sites. Direct application of NE or administration of AR agents can affect the activity of striatal neurons and release of DA in the striatum (Bevam et al., 1975; Fujimoto et al., 1981; Lategan et al., 1990).

5.2 LC innervation to midbrain dopaminergic neurons

The midbrain dopaminergic neurons in the SN and VTA also receive direct innervation from LC noradrenergic neurons (Fritschy & Grzanna, 1990; Jones & Moore, 1977; Jones & Yang, 1985; Phillipson, 1979; Simon et al., 1979; Swanson & Hartman, 1975). The SN and VTA regions have detectable levels of NET binding, also indicating direct noradrenergic innervation and some of the innervation is from the LC (Szot, Personal communications). The SN and VTA also have β-, α_1- and α_2-AR binding sites (Szot, Personal communication; Boyajian et al., 1987; Hudson et al., 1992; Lee et al., 1998; Rainbow et al., 1984; Rosin et al., 1996; Scheinin et al., 1994; Strazielle et al., 1999). The LC directly innervates and modifies the activity of midbrain dopaminergic neurons; the loss of LC noradrenergic neurons results in altered activity of dopaminergic neurons (Collingridge et al., 1979; Grenhoff et al., 1993, 1995; Grenhoff & Svensson, 1989, 1993; Guiard et al., 2008; Wang et al., 2010).

5.3 LC altered dopaminergic behavior

There have been several studies to indicate the ability of LC noradrenergic neurons to modulate dopamine-induced behavior, especially when LC noradrenergic neurons are reduced (Antelman & Caggiula, 1977; Archer & Fredriksson, 2006; Chopin et al., 1999; Grimbergen et al., 2009; Mavridis et al., 1991; Rommelfanger et al., 2007; Taylor et al., 2009; Villegier et al., 2003; Wang et al., 2010). In addition, reducing LC function alone by lesioning LC neurons can produce motor symptoms that are observed in PD (Grimbergen et al., 2009; Wang et al., 2010). In support of the LC lesion studies and the consequence of reduced NE content, DBH knockout mice, which do not synthesize NE, also exhibit PD motor symptoms with age (Rommelfanger et al., 2007). These data suggest the loss of LC noradrenergic function observed in PD may contribute to the motor symptoms of PD.

6. Neuroprotective effect of LC neurons on dopaminergic neurons

Since the noradrenergic nervous system experiences a loss of function before the dopaminergic system in PD (Braak et al., 2003b, 2006) and the noradrenergic nervous system innervates dopaminergic neurons in the SN and VTA (shown above); the noradrenergic nervous system could then affect the stability of dopaminergic neurons. There is data to support the hypothesis of a neuroprotective effect of the noradrenergic system upon dopaminergic neurons in animal models. To determine if the LC noradrenergic nervous system exerts a neuroprotective effect on dopaminergic neurons, a dopaminergic neurotoxin needs to be administered.

6.1 Animal models of PD

There are several different animal models of PD which have been described in detail elsewhere (Betarbet et al., 2002; Dauer & Przedborski, 2003; Jackson-Lewis & Przedborski, 2007; Luchtman et al., 2009) and are not the focus of this chapter. The classic PD symptoms induced by a variety of dopaminergic neurotoxins are reduced number of SN dopaminergic neurons and reduced amount of DA in the striatum. The most routinely used dopaminergic neurotoxins are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6OHDA). The choice of neurotoxin depends on the species of animal to be studied. MPTP is typically the neurotoxin used to reduce the number of dopaminergic neurons in the SN (and to a lesser degree the VTA neurons) in mice and monkeys. MPTP is

administered peripherally and depending on the dose and the number of times it is administered, a mild to severe degree of dopaminergic neuronal loss can be observed (Betarbet et al., 2002; Dauer & Przedborski, 2003; Jackson-Lewis & Przedborski, 2007; Luchtman et al., 2009). However, MPTP is not effective in rats (Jackson-Lewis & Przedborski, 2007). To reduce the number of SN dopaminergic neurons in rats, 6OHDA is administered directly into the medial forebrain bundle using stereotaxic surgery. The effect of 6OHDA in the SN is rapid and appears permanent (Walsh et al., 2011).

6.2 Enhanced LC function reduces dopaminergic neurotoxin-induced damage

6.2.1 Neuroprotective effect of enhanced noradrenergic function in tottering and NET transgenic mice

The tottering mouse has a mutation that results in hyperinnervation of noradrenergic terminals and increased concentration of NE throughout most regions of the forebrain. Administration of MPTP to these mutant mice has less of an effect on dopaminergic terminals in the striatum (i.e., loss of DA level) as compared to wild-type mice (Kilbourne et al., 1998). Another transgenic mouse that has enhanced noradrenergic function is the NET knockout mouse. NET knockout mice do not express the transporter protein for NE, which are localized specifically to noradrenergic neurons and responsible for removing NE from the synapse, resulting in enhanced NE in the synapse. Administration of MPTP to NET knockout mice, again, results in reduced damage to dopaminergic terminals in the striatum and DA levels in the striatum as compared to wild-type mice (Rommelfanger et al., 2004). These studies indicate that an enhanced noradrenergic system can protect dopaminergic neurons in the SN from damage.

6.2.2 Neuroprotective effect of AR agents

Another means of increasing noradrenergic function is to administer noradrenergic agonists. Administration of NET inhibitors to increase synaptic NE levels results in reduced dopaminergic damage on SN terminals in the striatum and DA levels, resembling the effect observed in the NET knockout mouse (Rommelfanger et al., 2004). Peripheral administration of α_2-AR agonists such as clonidine and detomidine also reduces MPTP-induced reduction in striatal DA levels, while administration of α_2-AR antagonists enhances MPTP-induced damage in mice (Fornai et al., 1995a). However, when 6OHDA is used as the dopaminergic neurotoxin in rats, the peripheral administration of α_2-AR antagonists reduces the loss of DA in the striatum (Srinivasan & Schmidt, 2004b, c), the opposite of what is observed in mice with MPTP. The ability of α_2-AR agents to either enhance or reduce damage on dopaminergic neurons could be attributed to the different species (rats versus mice) or the neurotoxin (MPTP versus 6OHDA) used. Another possible reason for the conflicting data of α_2-AR agents is the complexity of the α_2-AR. The α_2-AR receptor is composed of three different subtypes: α_{2A}-, α_{2B}-, and α_{2C}-AR. α_{2A}- and α_{2C}-ARs are localized on dendrites and terminals of noradrenergic neurons where they act as presynaptic autoreceptors to regulate the release of NE (L'Heureux et al., 1986; Van Gaalen et al., 1997; Kawahara et al., 1999), as well as postsynaptic receptors on dendrites and terminals of NE target cell that regulate the release of other neurotransmitters (heteroreceptors). α_{2A}-ARs are the most abundant α_2-AR subtype in the brain, comprising approximately 90% of all central α_2-ARs (Bucheler et al., 2002). The highest density of α_{2C}-AR is in the striatum, while α_{2B}-ARs have a very limited expression in the brain (Nicholas et al., 1993; Zeng & Lynch, 1991).

Clonidine and detomidine do not discriminate between the different subtypes, so it is unclear how these agonists affect noradrenergic function: reduced NE release and function by acting on presynaptic autoreceptors or enhancing NEs action at postsynaptic receptors. The same complexity exists for the effects of α_2-AR antagonists.

6.2.3 Summary

These studies indicate that increased noradrenergic function, either through genetic manipulation or pharmacologically, results in less damage to dopaminergic neurons by MPTP, indicating a neuroprotective effect of the noradrenergic nervous system on dopaminergic neurons. The major concern with these studies is that the enhanced noradrenergic function is not limited exclusively to the LC noradrenergic system. There is also the added complexity of the localization of the different noradrenergic receptors, pre- versus post-synaptically, and the differences in expression of AR between rats and mice (Szot, 2006) which may contribute to the conflicting results of α_2-AR agonists. Future studies could examine the ability of other AR agonists that act postsynaptically to modulate susceptibility of dopaminergic neurons to damage or determine if pharmacological agents produce a neuroprotective effect after direct administration into a specific brain region such as the striatum or SN.

6.3 Reduced LC function enhances susceptibility of dopaminergic neurons to damage

An easier approach in determining if the LC noradrenergic nervous system can affect the susceptibility of dopaminergic neurons to damage is to reduce the number of LC noradrenergic neurons and innervation to forebrain regions. This approach specifically targets the LC noradrenergic neurons, mimicking what is observed in PD. LC noradrenergic neuronal loss has been shown to occur with administration of 6OHDA directly into the LC and peripheral administration of N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP4).

6.3.1 DSP4 enhances susceptibility of dopaminergic neurons to damage

DSP4 has been considered a LC selective noradrenergic neurotoxin since 1980s. The determination that DSP4 was a selective LC neurotoxin is based on documented changes in terminal noradrenergic fibers in regions innervated mainly by the LC. The appeal of DSP4 as a noradrenergic neurotoxin over other methods (like 6OHDA) is that DSP4 can produce this central affect by peripheral administration. DSP4 produces a rapid, though transient, reduction in terminal NE concentrations in the frontal cortex, hippocampus and cerebellum (Grzanna et al., 1989; Harro et al., 1999a, b; Hughes & Stanford, 1996, 1998; Jonsson et al., 1981; Kask et al., 1997; Ross, 1976; Szot et al., 2011; Theron et al., 1993; Wolfman et al., 1994). As indicated earlier, these regions receive sole innervation from the LC (Aston-Jones et al., 1995; Jones & Moore, 1977; Loughlin et al., 1986a, b; Mason & Fibiger, 1970; Moore & Bloom, 1979; Olsen & Fuxe, 1971; Ungerstedt, 1971; Waterhouse et al., 1983) so the original hypothesis was that DSP4 affected only LC neurons. NET binding sites are also reduced in specific forebrain regions, indicating a loss of innervation from the LC (Cheetham et al., 1996; Szot et al., 2010). The hypothesis that DSP4 was a neurotoxin was supported by TH-IR which demonstrated a gradual loss of LC noradrenergic neurons after by DSP4 administration (Grzanna et al., 1989). Since these initial descriptions of DSP4 as a noradrenergic neurotoxin, there have been other publications suggesting that DSP4 does not result in a loss of LC noradrenergic neurons (Booze et al., 1988; Lyon et al., 1983; Matsukawa

et al., 2003; Robertson et al., 1993; Szot et al., 2010) and that DSP4 does not selectively affect LC noradrenergic terminals (Grzanna et al., 1989; Kask et al., 1997; Szot et al., 2010; Theron et al., 1993; Wolfman et al., 1994). Work in our laboratory indicated that DSP4 may affect noradrenergic terminals and specific ARs in many forebrain regions (not just regions innervated by the LC), but it does so without a loss of LC noradrenergic neurons (Szot et al., 2010). Despite the data that suggests DSP4 may not result in a loss of LC noradrenergic neurons, DSP4 does result in a temporary reduction in terminal NE levels in many forebrain regions.

Administration of DSP4 prior to methamphetamine, MPTP or 6OHDA into the medial forebrain bundle will increase the damage these dopaminergic neurotoxins exert on SN dopaminergic neurons and DA levels in the striatum (Fornai et al., 1995b, 1996, 1997; Marien et al., 1993; Srinivasan and Schmidt, 2003, 2004a). The enhanced susceptibility of dopaminergic neurons to damage from these dopaminergic neurotoxins is observed at a time when DSP4 results in a significant reduction in terminal NE levels. Administration of DSP4 after the dopaminergic neurotoxin does not enhance the susceptibility of dopaminergic neurons to damage (Fornai et al., 1997). These data indicate that a reduction in NE levels in forebrain regions will increase the susceptibility of dopaminergic neurons to damage. However, administration of MPTP to DBH knockout mice does not result in enhanced loss of SN neurons or DA levels in the striatum as compared to wild-type mice (Rommelfanger and Weinshenker, 2007). Administration of DSP4 prior to the administration of MPTP in the DBH knockout mouse does result in enhanced damage to dopaminergic neurons and terminals as compared to DBH knockout mice administered MPTP alone (Rommelfanger and Weinshenker, 2007).

6.3.2 6OHDA enhances susceptibility of dopaminergic neurons to damage

There are few studies examining the direct administration of the neurotoxin 6OHDA directly into those LC, though the few that do demonstrate a reduction in the number of LC noradrenergic neurons (Bing et al., 1991; Mavridis et al., 1991). Our laboratory has begun to examine the specificity of direct LC 6OHDA administration on LC neurons and lateral tegmental neurons as well as neurons in the SN and VTA. We have observed that direct administration of 6OHDA into the LC specifically reduces LC noradrenergic neurons, while there is no effect on SN or VTA dopaminergic neurons or on lateral tegmental neurons (data not shown).

There are two studies that have examined the ability of LC 6OHDA administration to increase MPTP-induced damage to dopaminergic neurons. Bing et al., (1994) examined the ability of LC 6OHDA to enhance MPTP-induced damage in the mouse, while Mavridis et al., (1991) examined LC 6OHDA in monkeys. Both of these studies demonstrated an enhanced susceptibility of dopaminergic neurons to damage following LC neuronal loss. Preliminary work in my laboratory has begun to examine the effects of 6OHDA administration into the LC of mice on the susceptibility of dopaminergic neurons to MPTP. We have examined the effect of MPTP (24 mg/kg, ip, twice, 2hrs apart) administered 3 days after bilateral administration of 6OHDA into the LC on LC, SN and VTA neurons. MPTP alone did not affect LC noradrenergic neurons, but MPTP alone significantly reduced DAergic neurons in the SN (28% reduced) with no effect on VTA neurons (7% reduced). However, the *combination* of 6OHDA + MPTP resulted in a further reduction in SN neurons (71% reduced) and a significant reduction in VTA neurons (54% reduced) (data not shown).

These data indicate that administration of the noradrenergic neurotoxin 6OHDA can increase the susceptibility of dopaminergic neurons to damage.

6.4 Summary

These data suggest that enhanced noradrenergic function can protect dopaminergic neurons from damage, while reducing noradrenergic function enhances the susceptibility of dopaminergic neurons to damage. The number of studies examining this important question are few, but the data indicates the LC noradrenergic nervous system can modulate the viability of dopaminergic neurons to damage. It is unknown why dopaminergic neurons in PD are reduced. The loss of dopaminergic neurons and the appearance of PD symptoms occur midway in the progression of the disorder, after the loss of LC noradrenergic neurons. Therefore, determining factors that can maintain the stability of dopaminergic neurons in the early stages of the disorder is imperative in preventing the loss of dopaminergic neurons and the onset of PD symptoms. Since LC neuronal loss occurs early in the progression of PD and is a prominent neuropathologic change in PD, an animal model examining the neuroprotective effect of the noradrenergic nervous system on dopaminergic neurons must exhibit reduced LC noradrenergic neuronal number, so DSP4 may not be the best animal model of LC neuronal loss. Future work will determine if there is a particular time following the loss of LC noradrenergic neurons that renders the dopaminergic neurons more susceptible to damage, or it may be that following administration of MPTP, animals with reduced LC function do not recover from the damage induced by MPTP.

7. Noradrenergic agents relieve L-DOPA-induced dyskinesia

7.1 Chronic L-DOPA therapy induces dyskinesia

In addition to the potential neuroprotective effect of the noradrenergic nervous system on dopaminergic neurons early in the progression of PD, the noradrenergic nervous system may also improve therapy of PD subjects. As indicated above, L-DOPA is the primary therapy in the treatment of PD motor symptoms. However, chronic treatment of L-DOPA in PD subjects results in permanent severe side effect, dyskinesia (abnormal involuntary movements). The incidence of dyskinesia in PD subjects increases with the length of time on L-DOPA therapy; 30% of patients experience dyskinesia after 4-6 years to 90% after 9 years (Rascol et al., 2000; Ahlskog & Muenter, 2001). The underlying mechanism behind L-DOPA-induced dyskinesia is thought to be extraphysiological DA release resulting in aberrant receptor signaling in the striatum; this enhanced dopaminergic signaling then dysregulates subsequent striatal output (Cenci, 2007, 2009; Winkler et al., 2002). Until a means of preventing the onset of PD occurs or a new treatment for PD that does not result in dyskinesia is found, adjunct pharmacological therapy with L-DOPA that prevents or reduces dyskinesia is the focus of future work in PD therapy.

7.2 AR antagonists reduce L-DOPA-induced dyskinesia

As indicated earlier, the different types of ARs (β-, α_1- and α_2-ARs) are localized to the striatum and AR agents can alter the activity of striatal neurons (see above). However, at the present time it is unclear if the loss of LC noradrenergic neurons early in the progression of PD contributes to the L-DOPA-induced overactivity of striatal neurons that ultimately results in dyskinesia (Marin et al., 2008) or how L-DOPA therapy affects noradrenergic

neurons (Figure 2). What is known is that α_2-AR agonists can facilitate movement by acting through the striatum (Hill and Brotchie, 1999). Therefore, α_2-AR antagonists have been studied as a potential adjunct therapy to reduce L-DOPA-induced dyskinesia. α_2-AR antagonists, yohimbine, idazoxan and fipamezole reduce L-DOPA dyskinesia in the MPTP and 6OHDA PD animal models and in Parkinsonian patients. These α_2-AR antagonists reduce L-DOPA-induced side effects without affecting the anti-parkinsonian effect of L-DOPA (Brotchie, 2005; Buck et al., 2010; Colosimo and Craus, 2003; Chopin et al., 1986; Gomez-Mancilla and Bedard, 1993; Grondin et al., 2000; Henry et al., 1999; Lundblad et al., 2002; Rascol et al., 2001; Savola et al., 2003). However, the anti-dyskinetic effect of α_2-AR antagonists may be limited to just L-DOPA; idazoxan did not reduce apomorphine-induced dyskinesia (Fox et al., 2001). The α_2-ARs are not the only receptor capable of modulating L-DOPA-induced dyskinesia. Because β-ARs are found in large concentrations in the striatum (see above), studies are now beginning to determine if β-AR antagonists, such as propranolol, can reduce L-DOPA-induced dyskinesia. These studies indicate that propranolol also reduces L-DOPA-induced dyskinesia (Goshima et al., 1991; Reisine et al., 1982; Carpentier et al., 1996; Dekundy et al., 2007). α_1-AR antagonist also reduces L-DOPA-induced dyskinesia; however, this receptor subtype has not been investigated to the same degree as α_2- and β-AR antagonists (Buck and Ferbeger, 2010).

8. Conclusion

The dopaminergic nervous system has been the major focus of research in PD for many years, and rightly so because it is the loss of dopaminergic neurons and function that is responsible for the appearance of the motor symptoms that define PD. However, the noradrenergic nervous system appears to play an important role in the progression of PD and in the therapy of PD. LC noradrenergic neurons are reduced early in the progression of PD, even before dopaminergic neurons. Animal models suggest that the loss of LC noradrenergic neurons will enhance the susceptibility of dopaminergic neurons to damage. Understanding the relationship of LC neuronal loss to enhanced dopaminergic susceptibility to damage introduces a time window in which pharmacological intervention could *prevent* the loss of dopaminergic neurons and the appearance of motor symptoms. But until this relationship is examined, the noradrenergic nervous system can be used to reduce Dyskinesia, the severe side effects of chronic L-DOPA therapy. These data indicate the importance of examining neurotransmitter systems other than DA and determining the role of transmitters, such as NE, in affecting PD.

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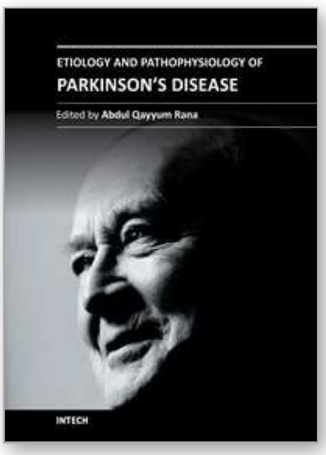

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This book about Parkinsonâ€™s disease provides a detailed account of etiology and pathophysiology of Parkinsonâ€™s disease, a complicated neurological condition. Environmental and genetic factors involved in the causation of Parkinsonâ€™s disease have 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 Parkinsonâ€™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 Parkinsonâ€™s disease.

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