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Research Report

Differential response of the central noradrenergic nervous system to the loss of locus coeruleus neurons in Parkinson's disease and Alzheimer's disease

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ABSTRACT

In Parkinson's disease (PD), there is a significant loss of noradrenergic neurons in the locus coeruleus (LC) in addition to the loss of dopaminergic neurons in the substantia nigra (SN). The goal of this study was to determine if the surviving LC noradrenergic neurons in PD demonstrate compensatory changes in response to the neuronal loss, as observed in Alzheimer's disease (AD). Tyrosine hydroxylase (TH) and dopamine β-hydroxylase (DBH) mRNA expression in postmortem LC tissue of control and age-matched PD subjects demonstrated a significant reduction in the number of noradrenergic neurons in the LC of PD subjects. TH mRNA expression/neuron did not differ between control and PD subjects, but DBH mRNA expression/neuron was significantly elevated in PD subjects compared to control. This increase in DBH mRNA expression in PD subjects is not a response to neuronal loss because the amount of DBH mRNA expression/neuron in AD subjects was not significantly different from control. Norepinephrine transporter (NET) binding site concentration in the LC of PD subjects was significantly reduced over the cell body region as well as the peri-LC dendritic zone. In PD subjects, the loss of dendrites from surviving noradrenergic neurons was also apparent with TH-immunoreactivity (IR). This loss of LC dendritic innervation in PD subjects as measured by TH-IR was not due to LC neuronal loss because TH-IR in AD subjects was robust, despite a similar loss of LC neurons. These data suggest that there is a differential response of the noradrenergic nervous system in PD compared to AD in response to the loss of LC neurons.

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1. Introduction

Parkinson's disease (PD) is a progressive and debilitating neurodegenerative disorder that currently affects 2% of the population over the age of 65 years and will only become more prevalent as the younger generations age. The hallmark symptom of PD, motor dysfunction, is the result of a significant loss of dopaminergic neurons in the substantia nigra (SN) (Damier et al., 1999; Gibb, 1991; Gibb and Lees, 1991). However, the SN is not the only region that demonstrates significant neuronal loss in PD. There is also a significant loss of noradrenergic neurons in the locus coeruleus (LC), which is equal to or greater than the neuronal loss observed in the SN (Bertrand et al., 1997; Cash et al., 1987; Chan-Palay and Asan, 1989; Hornykiewicz and Kish, 1987; Marien et al., 2004; Patt and Gerhard, 1993; Zarow et al., 2003). The consequence of this neuronal loss on the surviving noradrenergic nervous system is unknown. In PD, there is a significant reduction in DBH, the synthetic enzyme specific to noradrenergic neurons, in the cortex, suggesting a reduction in noradrenergic innervation (Gasper et al., 1991). However, a loss of noradrenergic neurons in the LC does not necessarily result in reduced noradrenergic function: in Alzheimer's disease (AD), another neurodegenerative disorder where there is a significant loss of noradrenergic neurons in the LC, the surviving LC noradrenergic neurons demonstrate several compensatory changes. The content of NE in terminal regions in 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; Tomlinson et al., 1981). Similar results were observed for 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). Recently, our laboratory showed that the remaining noradrenergic neurons in the LC of AD and a related dementing disorder, dementia with Lewy body (DLB), showed three different compensatory changes: (1) increase in the expression of tyrosine hydroxylase (TH) mRNA; (2) sprouting of dendrites into the peri-LC dendritic zone; and (3) sprouting of axonal projections into the hippocampus and prefrontal cortex (Szot et al., 2006, 2007).

In this study we determined if the surviving LC noradrenergic neurons in PD subjects compensate for the neuronal loss: mRNA expression for the key synthetic enzymes, TH and DBH, was measured by in situ hybridization in the LC of PD subjects and age-matched control subjects. In addition, DBH mRNA expression was measured in AD subjects to determine the response of the surviving noradrenergic neurons in AD and to compare these results with an earlier study measuring TH mRNA expression (Szot et al., 2006). These enzymes are important in the synthetic pathway for NE: TH converts tyrosine to L-DOPA; L-DOPA is converted to dopamine (DA) by aromatic amino acid decarboxylase, and

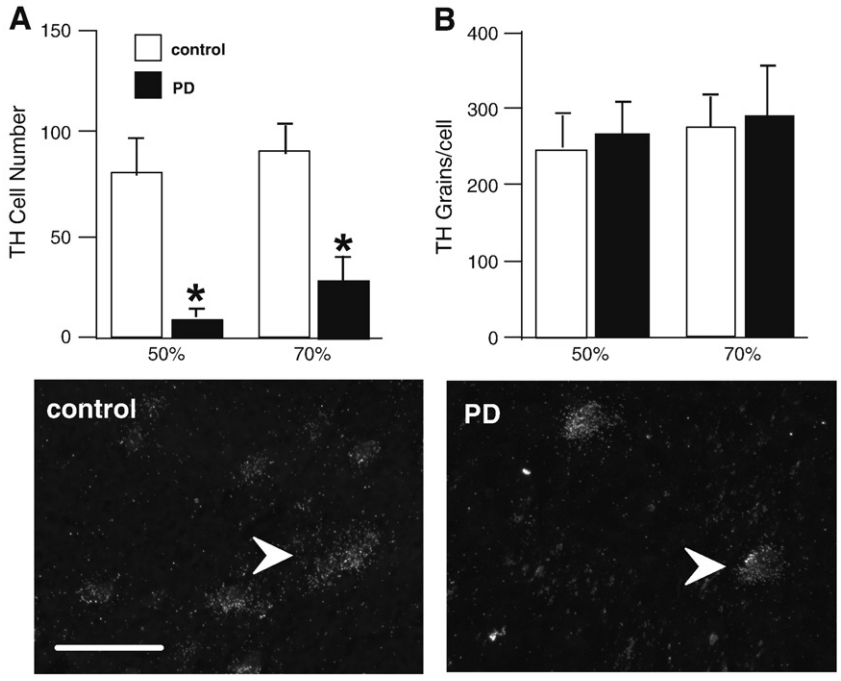

Fig. 1 – TH mRNA expression in the LC of age-matched control ($n=8$) and PD ($n=7$) subjects. (A) The number of TH positively labeled neurons at the 50% and 70% level of the LC of age-matched control and PD subjects. In PD subjects, there is a significant decrease in the number of TH positively labeled neurons at both levels of the LC (50% level $p=0.009$, 70% level $p=0.008$). (B) Expression of TH mRNA/neuron in the LC of control and PD subjects at the 50% and 70% levels. All labeled neurons that were counted as positively labeled were also quantitated for the amount of TH mRNA expression/neuron. There is not a difference in the amount of TH mRNA expression/neuron in PD subjects as compared to control age-matched subjects. The bottom two images are dark-field photomicrographs of TH mRNA-labeled neurons in age-matched control (bottom left) and PD (bottom right) at the 50% level of LC. Asterisk (*) indicates significant difference from age-matched control subjects. Arrow indicates a TH mRNA-labeled neuron. Scale bar=100 μm.