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BRAIN RESEARCH

Research Report

Microglial activation and age-related dopaminergic neurodegeneration in MPTP-treated SAMP8 mice

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ABSTRACT

Senescence-accelerated mouse prone 8 (SAMP8) has an early onset of senility and a shorter life span, providing with cognitive impairment. Contrasted with C57BL/6 mouse, which is most commonly used in the study of Parkinson's disease (PD), SAMP8 needs shorter period of breeding and might be good candidate for the investigation of cognitive impairment in PD. Studies had shown the increase of sensibility to 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) with aging in C57BL/6 mouse. However, the sensitivity of MPTP neurotoxicity depends on the strains of animal and the exact mechanisms of the progression of PD promoted by aging is lack of consensus. Here, we showed after MPTP injection, the spontaneous activity of both young (3-month-old) and old (6-month-old) SAMP8 decreased dramatically, and the old mice required longer recovery time. Immunohistochemical and immunoblot analysis revealed that old mice displayed significant reductions in the dopaminergic neuron numbers and tyrosine hydroxylase (TH) protein. Microglia protein (CD11b) in the striatum of old mice increased more pronouncedly than that in the young mice from 24 h to 3 days. Inducible nitric oxide synthase (iNOS) in the striatum remarkably increased, however, no discernible difference between the two groups was found. These results suggested that the sensibility to MPTP increased with aging in SAMP8. A greater increase of microglial activation in old mice may be a possible mechanism to explain how advancing age predisposes the dopamine system to parkinsonism. The MPTP-SAMP8 model will start a new consideration for the study of PD.

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Abbreviations: PD, idiopathic Parkinson's disease; SAMP8, senescence accelerated mouse prone8; MPTP, 1-methyl-4-phenyl-1 2, 3, 6-tetrahydropyridine; iNOS, inducible nitric oxide synthase; TH, tyrosine hydroxylase; SN, substantia nigra; DA, dopamine; TH-ir, TH-immunoreactive; OD, optical densities; MPP, 1-methyl-4-phenylpyridinium

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1. Introduction

Parkinson's disease (PD) is an age-related neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra (SN) (von Bohlen Und Halbach O, 2005). It has been well established that aging is the most prominent risk factor for PD (Collier et al., 2007). The 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) mouse model has been widely used to study PD. Some studies have shown that the neurotoxicity observed in MPTP mouse is age-dependent (Sugama et al., 2003; Ohashi et al., 2006). In an acute MPTP-PD model, old C57BL mice (9-12 months old) are more sensitive to neurotoxicity than young mice (3 months old), with more severe loss of dopaminergic neurons. Intraperitoneal administration of MPTP to old C57BL mice (14–15 months old) led to a remarkable loss of dopaminergic neurons with a marked decrease in dopamine levels. However, these aged mice have a long period of breeding, the mechanism by which aging predisposes the nigrostriatal dopaminergic system to parkinsonism remains largely unknown.

Recently, an increasing number of studies in the animal models of PD, including MPTP models, have suggested that the activation of microglia play an important role in dopaminergic neurodegeneration (Sugama et al., 2003; McGeer and McGeer, 2004; Herrera et al., 2005; Liu, 2006; Watanabe et al., 2008). Researches have also shown that inhibiting of microglial activation could relieve the degeneration of dopaminergic neurons in animal models of PD (He et al., 2001; Wu et al., 2002; Kawasaki et al., 2008). Nitric oxide (NO), an uncharged and lipophilic molecule that is toxic to neurons, is one of the pro-inflammatory factors released by microglia. Inducible nitric oxide synthase (iNOS) has been shown to be up-regulated in microglia in PD and in MPTP-treated mice (Knott et al., 2000; Wu et al., 2002, 2003), resulting in elevated NO production. The expression of iNOS in activated microglia contributes to the death of dopaminergic neurons in both MPTP toxicity and PD (Dehmer et al., 2000). Whether or not microglia and iNOS contribute to the age-dependent damage of the nigrostriatal system is unclear.

The SAMP8 mouse displays early-onset senility (in the 4–6 months maturation period), and is characterized by learning and memory impairment, as well as affective disturbance (Kawamata et al., 1997; Miyamoto, 1997; Takeda et al., 1997). The parkinsonian syndrome includes psychiatric cognitive disturbances and movement syndrome (Taylor et al., 1986; Levin et al., 1989; Cooper et al., 1991). So far, no other PD animal models exhibit these characteristics. SAMP8 mouse used in the research of PD may contribute to shorten the cycle of study, and may be useful for the investigation of psychiatric and cognitive impairment of PD. But the sensitivity of MPTP neurotoxicity depends on the strains of animal (Bove et al., 2005; Schmidt and Ferger, 2001; Sedelis et al., 2001). We previously reported that MPTP can induce a marked decrease in striatal dopamine (DA) levels and a loss of dopaminergic neurons in the SN of SAMP8 mice Liu et al. (2008). In the present study, the MPTP challenged SAMP8 mice model was used to study the influence of aging on the nigrostriatal system. In addition, the microglial activation as well as the expression levels of TH, CD11b and iNOS were analyzed in relating to the age-dependent impairment of the dopaminergic system.

2. Results

2.1. Spontaneous motor activity

Only three mice from the old MPTP group died during the course of this study. The spontaneous motor activity was significantly different between the MPTP groups and the control groups. In MPTP treated groups, the spontaneous motor activities for both young and old mice groups reached the lowest point at 6 h after treatment (P 0.05). However, young mice recovered 48 h after the first MPTP injection, while the old mice never recovered throughout the whole course of the study (7 days, P 0.05) (Fig. 1).

2.2. Dopaminergic neurons and TH protein in the SN

2.2.1. TH immunostaining

A loss of dopaminergic neurons was observed in the SN of the MPTP-treated SAMP8 mice (Table 1 and Fig. 2A). In young mice, the loss of TH-positive neurons was visible at 6 h (7.06%, $P=0.235$), and became significant after 24 h. The percentages recorded are 24 h (12.79%, $P<0.05$), 3 days (22.49%, $P<0.01$), and 8 days (42.39%, $P<0.001$). In old mice, TH-positive neuron loss became significant as early as 6 h (14.23%, $P<0.05$). And the percentages recorded for the later time points are 24 h (23.85%, $P<0.01$), 3 days (36.77%, $P<0.001$), and 8 days (45.90%, $P<0.001$). In comparison of the two MPTP groups, with the significant progression of dopaminergic neuron loss in young mice occurred most prominently from days 3 to 8 (3 days vs. 8 days, $P<0.01$), while in old mice, the same consequence occurred much earlier with the most dramatic progression from 24 h to 3 days (24 h vs. 3 days, $P<0.05$). In summary, according to TH immunostaining results, the old MPTP-SAMP8

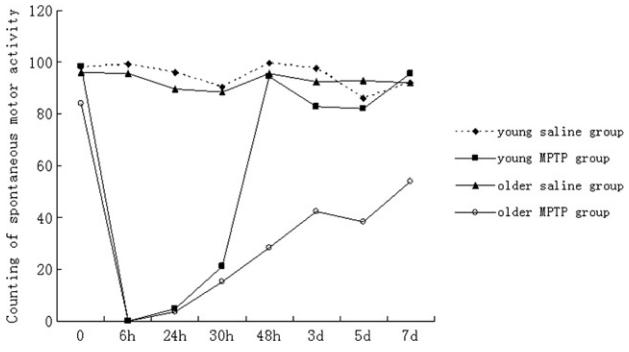

Fig. 1 – Spontaneous motor activity decreased after MPTP treatment in SAMP8 mice. The spontaneous motor activity reached its lowest point in 6 h ($P<0.05$) for both age groups, and recovered 48 h after the first MPTP injection in the young mice, while old mice never recovered throughout the period of investigation.