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BRAIN RESEARCH

Research Report

Increased 8-OHdG levels in the urine, serum, and substantia nigra of hemiparkinsonian rats

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ABSTRACT

8-Hydroxy-2′-deoxyguanosine (8-OHdG), the predominant marker of oxidative DNA damage, may be a good biomarker for monitoring the progression of Parkinson's disease (PD). Unfortunately, there are no basic laboratory data examining 8-OHdG levels in animal models of PD. In this study, we demonstrate that rats lesioned with 6-hydroxydopamine (6-OHDA) in the medial forebrain bundle display significantly elevated 8-OHdG levels in urine, serum, and substantia nigra, but not cerebrospinal fluid and striatum, compared to sham controls. These increments in 8-OHdG levels were detected at 2 days, but not at 7 days after the lesion suggesting that oxidative stress is restricted to the acute phase of 6-OHDA neurotoxicity. The present results support 8-OHdG as a biomarker that may aid both in the diagnosis and in the documentation of progression in PD.

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1. Introduction

Parkinson's disease (PD) remains a clinical diagnosis based on presenting symptoms, a thorough history and neurological examination (Sethi, 2002). In the very early stage of the disease, PD can be more difficult to diagnose and, in many cases, misdiagnosed. Radiotracer imaging techniques, such as positron emission tomography, are helpful to detect reduced ^{18}F-dopa uptake into the nigrostriatal dopaminergic system (Poewe, 1993); however, this technology is not widely available and is relatively expensive. To date, critical biomarkers of PD have not been established to aid clinicians in making the diagnosis or in following the disease progression. Recent studies have demonstrated increased 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels in the serum and cerebrospinal fluid (CSF) (Kikuchi et al., 2002), and urine (Sato et al., 2005) of PD patients, indicating that 8-OHdG may be a useful biomarker in tracking PD progression. These observed increases in 8-OHdG in PD, which were also found in multiple system atrophy (Kikuchi et al., 2002), parallel previous reports of increased 8-OHdG levels in Alzheimer's disease (Lovell et al., 1999; Mecocci et al., 1994) and amyotrophic lateral sclerosis (Ferrante et al., 1997). Until now, however, 8-OHdG levels have not been studied in PD animal models. Here, we found that 6-hydroxydopamine (6-OHDA)-lesioned rats displayed elevated 8-OHdG levels in urine, serum, and substantia nigra, but not in CSF and striatum.

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Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; PD, Parkinson's disease; CSF, cerebrospinal fluid; MSA, multiple system atrophy patients; AD, Alzheimer's disease; 6-OHDA, 6-hydroxydopamine

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2. Results

2.1. 8-OHdG level in urine, serum and CSF

Urine and serum 8-OHdG levels at 2 days post-6-OHDA-lesion [urine: 4.3±0.8 ng/mg creatinine (115% increase to sham controls); serum: 9.6±0.4 ng/ml (30% increase to sham controls)] were significantly higher than those of sham controls and 6-OHDA-injected rats at 7 days post-lesion, respectively (urine: 2.0±0.4 and 1.7±0.2 ng/mg creatinine, $F_{(2,12)}=7.9$, $p=0.0066$; post-hoc p values<0.05; serum: 7.4±0.4 and 7.3±0.4 ng/ml, $F_{(2,12)}=10.9$, $p=0.002$; post-hoc p values<0.05, Fig. 1). However, the 8-OHdG level in CSF at 2 days post-6-OHDA-lesion (3.9±0.2 ng/ml, 25% increase to sham controls) was not significantly higher than those of sham controls and 6-OHDA-injected rats at 7 days post-lesion (3.1±0.3 and 3.6±0.3 ng/ml, respectively; $F_{(2,12)}=2.5$, $p=0.14$, Fig. 1).

2.2. 8-OHdG level in the substantia nigra and striatum

Levels of 8-OHdG in the lesioned substantia nigra of rats at 2 and 7 days post-6-OHDA-lesion (30.9±1.9 and 30.4±3.4 ng/mm^3, respectively) were significantly higher than those of the intact side (23.7±0.6 and 25.1±1.5 ng/mm^3 at days 2 and 7, respectively) ($F_{(2,12)}=4.7$, $p=0.032$; post-hoc p values<0.01, Fig. 2). The ratio of the 8-OHdG level of the lesioned substantia nigra to the intact side of 6-OHDA-injected rats at 2 days post-lesion (1.3±0.07), but not at 7 days post-lesion (1.2±0.07), was significantly higher than that of sham controls (1.0±0.03) ($F_{(2,12)}=5.9$, $p=0.017$; post-hoc p values<0.05, Fig. 2). The 8-OHdG levels in the striatum of the lesioned side of the rats at 2 and 7 days post-6-OHDA-lesion (4.3±0.32 and 4.2±0.13 ng/mm^3, respectively) did not significantly differ from those of the intact side (3.7±0.13 and 4.1±0.22 ng/mm^3 at days 2 and 7, respectively) ($F_{(2,12)}=1.5$, $p=0.26$, Fig. 2). Similarly, the ratio of

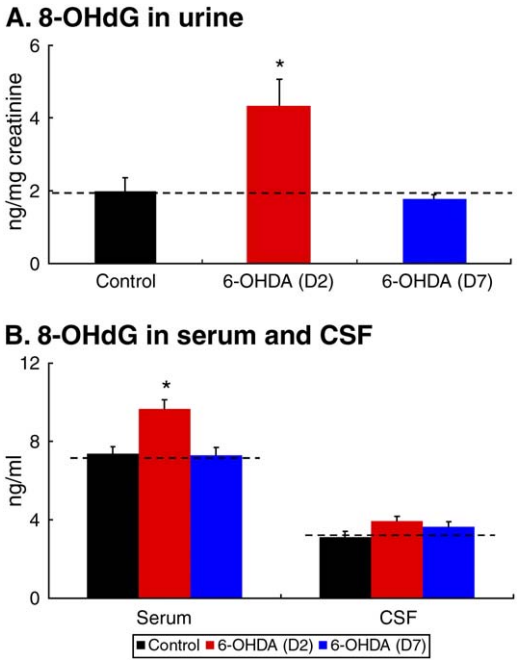

Fig. 1 – 8-OHdG levels in urine, serum, and CSF after 6-OHDA lesion. (A) The level of 8-OHdG in the urine of 6-OHDA-lesioned rats at 2 days post-lesion is significantly higher than that of sham controls and 6-OHDA-lesioned rats at 7 days post-lesion. *$p<0.05$. Data are shown as mean values (ng/mg creatinine)±SE. Dashed line indicates the level of normal rats. (B) Serum, but not CSF, level of 8-OHdG in 6-OHDA-lesioned rats at 2 days post-lesion is significantly higher than that of sham controls and 6-OHDA-lesioned rats at 7 days post-lesion. *$p<0.05$. Data are shown as mean values (ng/ml)±SE. Dashed line indicates the level of normal rats.

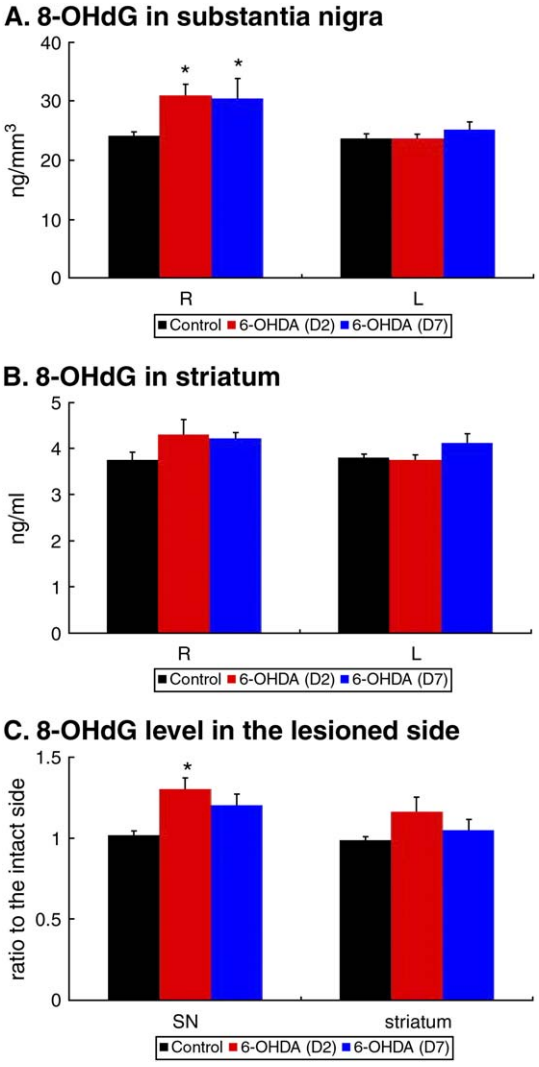

Fig. 2 – 8-OHdG levels in the substantia nigra and striatum. (A and B) The 8-OHdG level in the lesioned substantia nigra (A), but not striatum (B), is significantly higher than that of the intact side at 2 and 7 days post-6-OHDA lesion. *$p<0.05$. Data are shown as mean values (ng/mm^3)±SE. (C) The ratio of the lesioned substantia nigra, but not striatum to the intact side of 6-OHDA-lesioned rats at 2 days post-lesion is significantly higher than that of control rats, but not that of lesioned rats at 7 days post-lesion. *$p<0.05$. Data are shown as mean values±SE.

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