Chapter

The Striatal DNA Damage and Neurodegenerations

Huifangjie Li and Jinbin Xu

Abstract

Reactive oxygen species (ROS) are produced during normal metabolic reactions in living cells. ROS causes oxidative damage to many types of biomolecules. An age-related increase in oxidative damage to DNA and RNA has been described in the human neurons, which play a vital role in the progression of age-associated neurodegeneration. As dopamine metabolism is believed to be the primary source of ROS, oxidative insults correlate with dopamine levels in the striatum during the progression of neurodegenerative diseases. Parallel changes in dopamine concentrations and vesicular monoamine transporter 2 (VMAT2) binding densities in the striatum were observed. Besides Fenton oxidation taking place, the packing of cytosolic dopamine into synaptic vesicles by VMAT2 inhibits its autoxidation and subsequent decay of dopaminergic neurons. The female bias in the DNA damage in the late-stage Parkinson disease (PD) patients suggests that the sex-determining region of the Y chromosome (SRY) genes are critically involved. ROS are involved in regulating the rate of the aging procession in healthy cohorts and an increased life span of patients with neurodegenerative diseases via stimulation of protective stress responses. Moreover, the DNA repair pathway's mechanism, as genetic modifiers determine the age at onset through a ROS-inducing mutation.

Keywords: DNA damage, striatum, neurodegenerative diseases, dopamine, sex, age

1. Introduction

Oxidative damage can come from harmful environments such as chemical agents and ionizing radiation, but the major oxidative damage is also caused by internally sourced reactive oxygen species (ROS) generated from the natural metabolic processes in living cells. As the brain has a relatively higher oxygen demand and lower levels of antioxidants than other organs, ROS generates mainly DNA damage in the brain [1]. Numerous studies show that the accumulation of neuronal DNA damage contributes to the progress of aging [2]. DNA bases frequently undergo lesions through modification by alkylation, oxidation, and deamination [3]. To protect against these destructive adducts, cells have developed an antioxidant defense system to be expressed by enzymes involved in base excision repair (BER). The imbalance between clearance and generation of ROS plays a critical role in disease pathogenesis. Except for healthy aging, insufficient DNA repair has been tightly associated with neurodegenerative disorders such as Alzheimer disease (AD), Parkinson disease (PD), and amyotrophic

lateral sclerosis (ALS) [4–9]. The elevated DNA strand breaks and the decreased DNA double-strand breaks (DSBs) repair proteins have been described in AD brains.

Additionally, the increase in β-amyloid (Aβ) and neurofibrillary tangles (NFTs) is closely linked to decreased oxidative damage—an early event in AD that decreases with disease progression [10]. What is more, the lesions to mitochondrial, a major source of ROS, have been reported in the PD cases, and mitochondrial dysfunctions have been associated with the disease pathophysiology. Historically, the first investigation involving mitochondria in PD relates to the observation that the presence of an impairment of complex I in the different forms of PD and Parkinsonism [11]. Dementia with Lewy bodies (DLB), Parkinson disease dementia (PDD), and PD have been aggregated conceptually as Lewy body disease (LBD) [12].

Striatal dopaminergic dysfunction probably is involved in both AD and LBD, while degeneration of nigrostriatal dopaminergic neurons is the classic pathology of PD; striatal dopaminergic dysfunction may also promote the motor manifestations of AD. The striatum consists of several subregions—caudate and putamen. The caudate nucleus is essential in many behaviors, including procedural learning and working memory; the dorsal posterior putamen receives its primary input from the motor and sensorimotor cortices and regulates the motor circuits [13–15]. Dopamine generates hydroxyl radical (•OH) through Fenton reactions in the presence of iron, which is believed to be responsible for the oxidative damage to lipids, proteins, and DNA in living cells and dopaminergic neurons [16]. Besides, as a chelator, dopamine can form different complexes with Fe(II) and Fe(III), decreasing catalytic productions of ROS [17]. Dopamine compartmentalization has been described by the vesicular monoamine transporter 2 (VMAT2)—correlates with dopaminergic neurons' vulnerability in Parkinsonism neurodegeneration [18]. There are close interactions among oxidative damage and dopamine concentration, and the antioxidant role of VMAT2 should be given more attention. Oxidative stress induced by genetics has been linked to the Y-chromosome gene products that modulate dopamine biosynthesis and motor function [19]. Further, DNA damage is associated with acceleration of the rate of aging, causing a variety of early symptoms such as gray hair, kidney disease, cataracts, osteoporosis, and neuronal atrophy [20]—factors which determine the health or disease people's life span and age at the onset of diseases.

Therefore, it is clear that there is an appreciable need for a better understanding of the correlations between oxidative damage and neurodegenerations. In this chapter, the striatal DNA damage was first focused, and its brain region concentrations in neurodegenerative diseases will be discussed with parallel changes of dopamine levels and VMAT2 densities. Moreover, original data on the association among striatal DNA damages, sex, life span, and the age of onset of diseases in neurodegenerative patients will be presented.

2. Oxidative damage of DNA in the striatum from patients with neurodegenerative diseases

It is widely recognized that 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) and 8-oxo-7,8-dihydroguanosine (8-oxo-G) may act as biomarkers of oxidative damage to DNA and RNA, respectively [1]. Studies by Li et al. have reported the levels of DNA adducts in the caudate and putamen of the disease groups and age-matched controls [21]. Compared to controls, remarkable reductions in DNA

oxidation adducts were observed in the caudate of PD and DLB brains, including males and females. However, in the caudate of AD brains, these levels were elevated. This finding was especially pronounced for male AD patients, as adduct levels were 36% elevated compared to controls (**Figure 1**). The concentrations of 8-oxo-dG in the putamen of the disease groups were similar to the controls. Comparing between caudate and putamen, there were impressive elevations in adduct levels in the caudate, especially for the AD brains. These data indicate that the caudate is more vulnerable to DNA damage than the putamen in advanced AD patients.

RNA bases are more exposed and vulnerable to oxidative damage than DNA as they are not protected by hydrogen bonding and specific proteins. RNA oxidation has been described as a "steady-state" marker of oxidative lesions [22]; however, DNA oxidation has been believed to be a historical marker of oxidative damage during disease pathogenesis and aging progression [23]. Increased 8-OHdG levels have been documented in PD patients [24–26], but as shown in **Figure 1**, a noticeable reduction of DNA oxidation adducts in the caudate was observed in the late-stage LBD brains. It was not unique; the urinary concentration of 8-OHdG in the MFB 6-hydroxydopamine lesion model started to elevate at day 3 with a significant increase to day 7 and gradually back to baseline at day 42 [27]. The increased 8-oxo-dG levels in the caudate of AD brains connected with the increase in dopamine levels of the same cases. These phenomena are most likely due to the Fenton reactions taking place—in response to dopamine release and dopamine compartmentalization by VMAT2 [28].

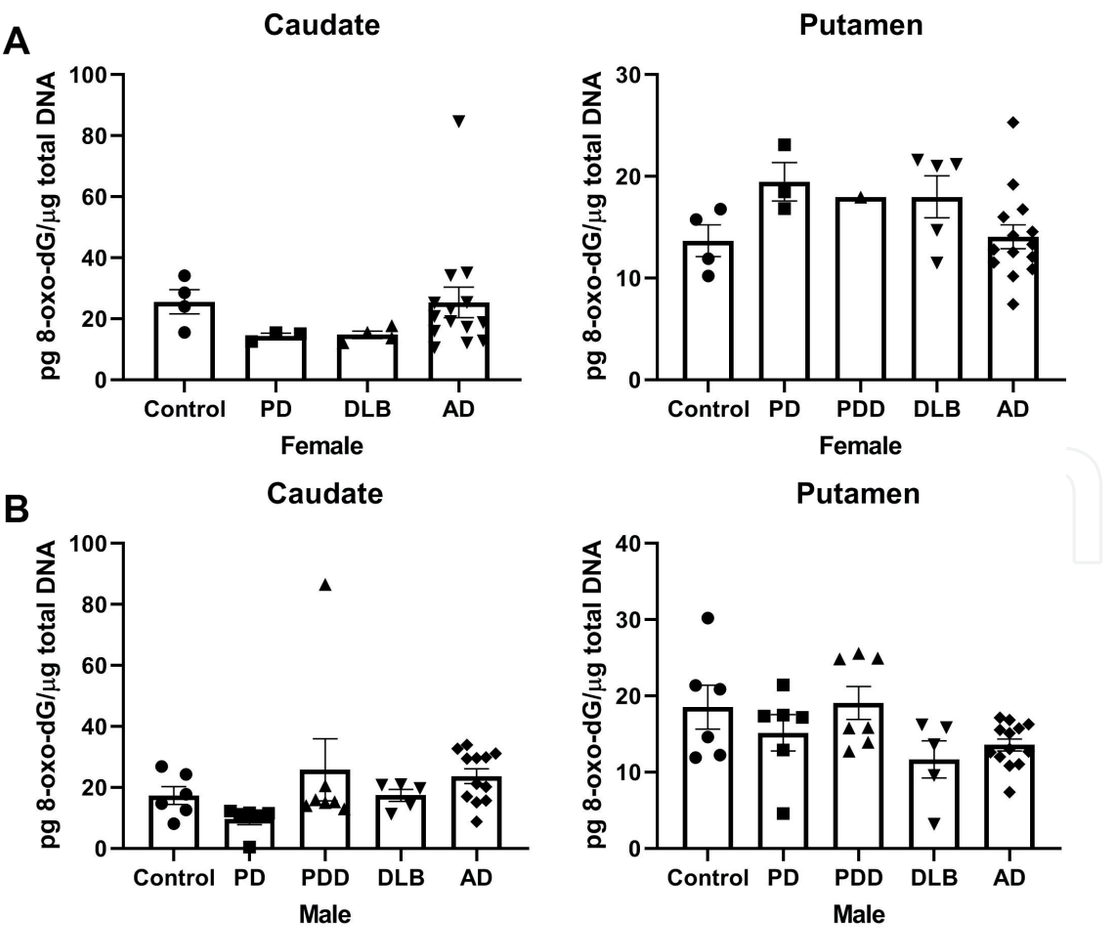


Figure 1.
8-oxo-dG levels in the caudate and putamen of patients with diseases (PD: n = 10, PDD: n = 7, DLB: n = 10, and AD: n = 26) and age-matched controls (n = 10). Values shown are means ± SEM as the concentration of 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) (pg) per total DNA (μg). (a) Female and (b) male.

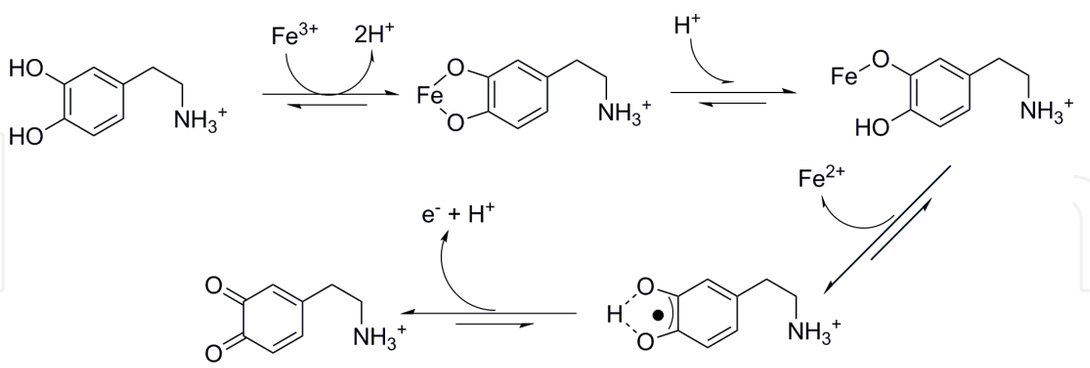
3. Interactions between oxidative damage and dopamine in the striatum of patients with neurodegenerative diseases

There are three biologically critical free radicals in our body, $O_2^{\bullet-}$, •OH, and $NO^{\bullet}$, mainly produced through Fenton oxidative reaction. Fenton reactions are catalytic oxidation reactions starting with transition metal ions, either iron or copper, and yielding both the hydroxyl radical (•OH) and higher oxidation states of the iron [29].

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {}^{\bullet}OH + OH^{-} \quad (1)$$

$$Fe^{3+} + H_2O_2 \rightarrow Fe^{2+} + {}^{\bullet}OOH + H^{+} \quad (2)$$

The relatively large amount of hydroxyl radical attacks adjacent to mitochondrial DNA strands and cytoplasmic RNA single-strands consequently produce an amount of oxidative adducts [29]. It is also critical to note that dopamine is metabolized enzymatically to produce a mass of H_2O_2 and, ultimately, dihydroxyphenylacetate, conversely promoting the dopaminergic exposure neurons to oxidative lesions. Put it another way, dopamine and related catechol are vulnerable molecules that can oxidize in the presence of transition metals to yield O_2^{-}, playing an essential role in nucleic oxidation as a major ROS source. O_2^{-}, a product of catechol autoxidation, can reversely oxidize catechol [30]. Either spontaneously or enzymatically, O_2^{-} can yield H_2O_2 and then •OH in the presence of transition metals [11]. The imbalance between clearance and generation of ROS promotes progressive dysfunction or increased death of dopaminergic neurons. Also, dopamine affects as a good metal chelator and electron donor and is capable of capturing iron and manganese [17]. Fe^{3+} has been reported as a catalyst for autoxidation of dopamine via the following mechanism [31]:



This mechanism can be proved further by a significant negative correlation between dopamine levels and 8-oxo-dG levels in the caudate of AD patients (**Figure 2**). Combined with a significant negative correlation between 8-oxo-dG levels and VMAT2 density in the same brain area from AD cases (**Figure 3**), these results are most likely owning to Fenton oxidation reactions taking place in the caudate from AD brains, which was believed to be a response to dopamine concentration and dopamine compartmentalization by VMAT2. As shown in **Figure 2**, dopamine concentrations in the caudate and putamen of disease patients and controls did not significantly differ. However, there were trends of decreasing and increasing dopamine levels in the LBD and AD patients, especially for the female cohorts.

PD has been described to be associated with both increased levels of nigral iron—a catalytic agent for yielding •OH—and enhanced Mn superoxide dismutase activity. As the midbrain levels of reduced glutathione were diminished, there was evidence of increased oxidative damage in the midbrain of PD patients, including not only lipid peroxidation, protein oxidation, oxidation of DNA, but also catechol oxidation in the same brain area of PD cases [11].

As shown in **Figure 3**, similar changes in VMAT2 density in the caudate and putamen are in line with the 8-oxo-dG and dopamine levels of the same cohorts. Compared to the controls, lower VMAT2 binding levels were found in the caudate from both female and male LBD cases. Diversely, a significant increase in VMAT2 density in female and male AD patients was observed. We can see significant negative correlations between 8-oxo-dG levels and VMAT2 density in the caudate (r_s = −0.451, p = 0.027) and putamen (r_s = −0.516, p = 0.024) of AD patients, as well as in the caudate (r_s = −0.683, p = 0.042) of PD patients. It might give

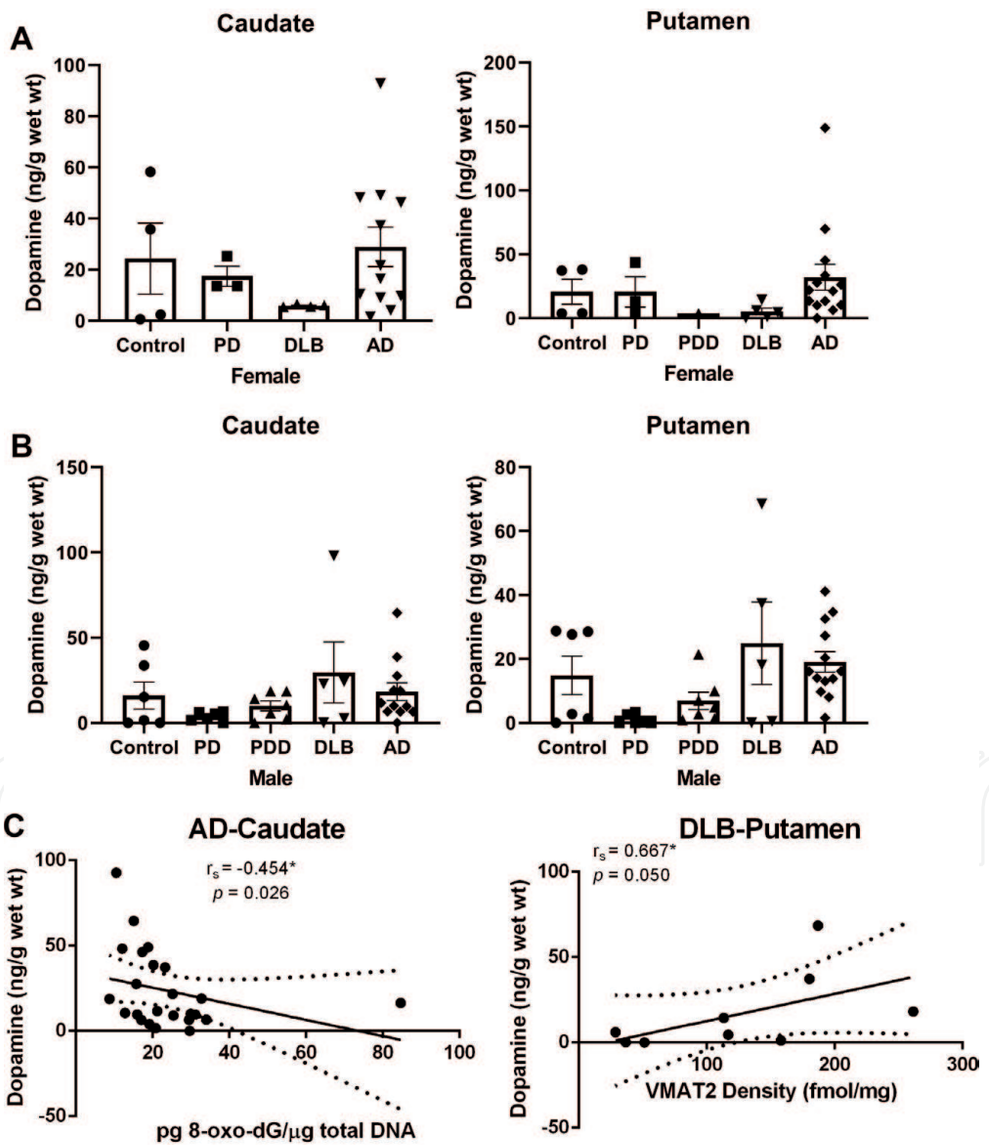


Figure 2.
Concentration of dopamine in the caudate and putamen from patients with diseases (PD: n = 10, PDD: n = 7, DLB: n = 10, and AD: n = 26) and age-matched controls (n = 10). (A) Female and (B) male. The values shown are means ± SEM. (C) Concentration of dopamine versus level of 8-oxo-dG in the caudate from diseases brains, significant association was observed only in the AD group (p = 0.026); concentration of dopamine versus VMAT2 expression in the putamen from diseases brains, significant association was observed only in DLB group (p = 0.050). r_s, the Spearman's rank correlation coefficient.

evidence that the reduction of vesicular storage increased dopamine release and then was conductive to produce hydrogen peroxide from MAO-catalyzed dopamine metabolism [32].

To better understand the correlations between oxidative damage and dopamine storage abilities, the spatial control of dopamine by VMAT2 and the antioxidation role of VMAT2 should be further elucidated. Bearing in mind the portrayal of oxidative lesions in the pathogenesis of PD, packing of cytosolic dopamine into synaptic vesicles by VMAT2 inhibits its autoxidation and the subsequent degeneration of dopaminergic neurons [33]. This theory conforms to the negative correlations observed between oxidative damage and VMAT2 density in striatum of both AD and PD patients. Reduced dopamine levels attenuated its uptake and transport functions by changing dopamine turnover. Thus,

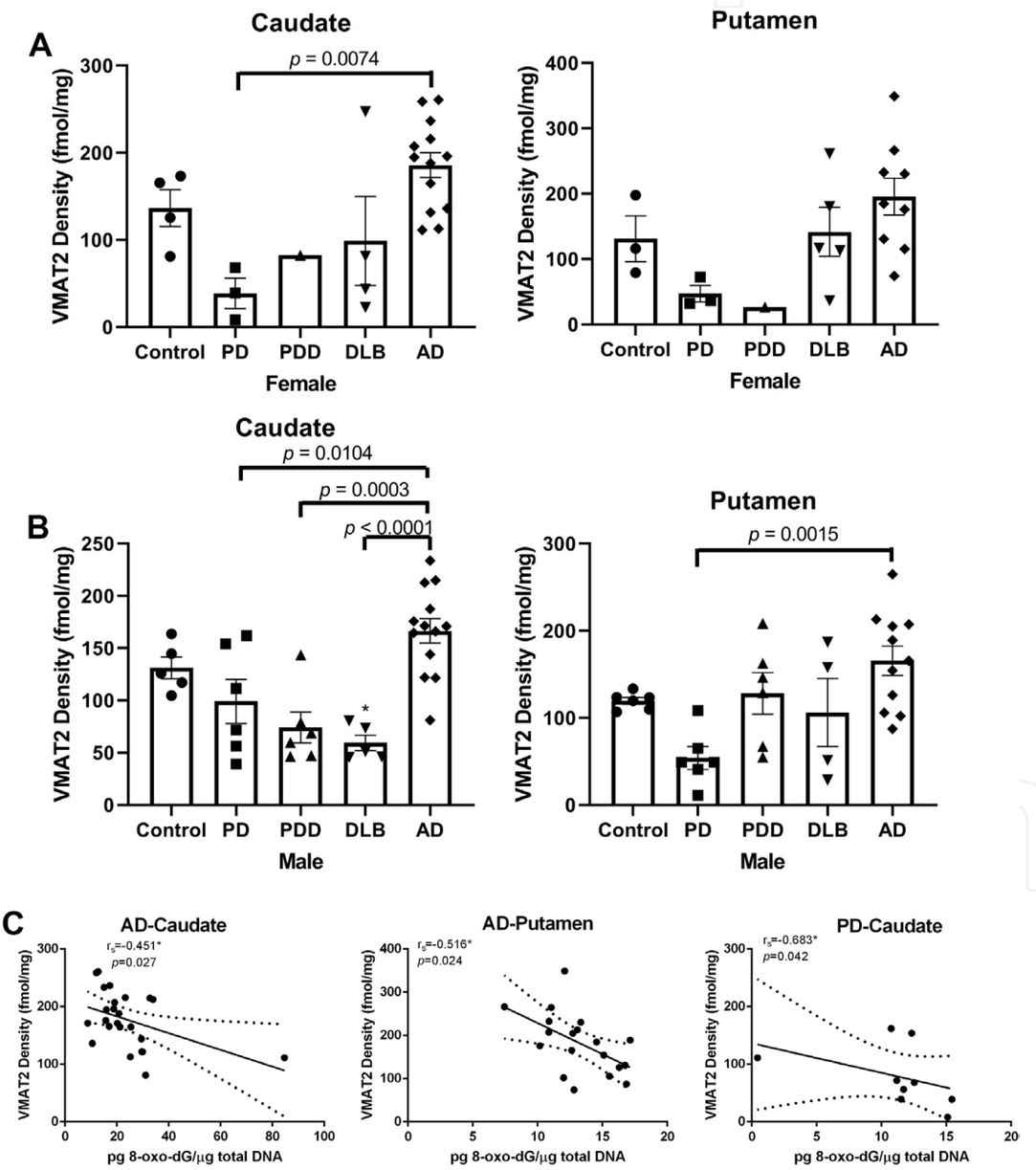


Figure 3.
*Quantitative autoradiographic analysis of VMAT2 density (fmol/mg) in the caudate and putamen from patients with diseases (PD: n = 10, PDD: n = 7, DLB: n = 10, and AD: n = 26) and age-matched controls (n = 10). (A) Female and (B) male. The values shown are means ± SEM. Statistical significance between two disease groups are indicated with brackets and corresponding p-values. A p value of <0.05 was considered significant: * indicates p < 0.05 versus the controls. (C) Density of VMAT2 as concentration of 8-oxo-dG in the caudate and putamen from AD brains (p = 0.027 and p = 0.024, respectively) as well as that in the caudate from PD brains (p = 0.042). Rs, the Spearman's rank correlation coefficient.*

VMAT2 expression correlates with the severity of Parkinsonism and cognitive impairment in DLB [18, 34]. The inhibition of dopamine metabolism by MAO-B attenuates hydrogen peroxide production, as a two-edged sword, it also increases the risk of dopamine autoxidation and subsequent augmentation of the cytosolic dopamine pool [32].

4. The interactions between oxidative damage in the striatum, sex, life span, and the age of onset of diseases in neurodegenerative patients

Many neurological diseases show significant sex differences in their susceptibility, severity, and progression [35, 36]. Specifically, a male bias has been found for disorders such as PD and attention-deficit hyperactivity disorder (ADHD), both of which are associated with abnormal levels of dopamine [37–39]. Considerable studies have supported the hypothesis that gonadal sex steroid hormones, especially estrogen, act as protectors in females by modulating dopamine release, metabolism, and dopamine receptors' activity. However, there is numerous evidence that genetic factors, especially sex-specific genes, influence either healthy or diseased dopamine systems [40–42].

As shown in **Figure 4**, Kendall's tau_b analysis revealed a significant positive correlation between sex and 8-oxo-dG levels in the caudate of PD cases. The result indicates that there is a sex difference concerning DNA damage in late-stage PD patients. Postmortem brain studies have revealed that the expression of PD-related genes in the substantia nigra pars compact (SNc), such as α-*synuclein* and *PINK-1*, is higher in men than women [43]. Sex-chromosome genes are critically involved, particularly the sex-determining region of the Y chromosome (*SRY*) gene [44]. The dopaminergic toxin, 6-hydroxydopamine (6-OHDA), has been described to significantly elevate *SRY* mRNA expression in human male dopamine cells, accompanied by an increase in the expression of GADD45γ, a DNA damage-inducible factor gene and a known *SRY* regulator. Interestingly, SRY upregulation initiated by dopamine cell damage is a protective response in males; however, the effect diminishes significantly with the gradual loss in dopamine cells [19].

DNA damage may be unique in its ability to promote multiple symptoms associated with old age. Exposure of rodents to ionizing radiation leads to the premature

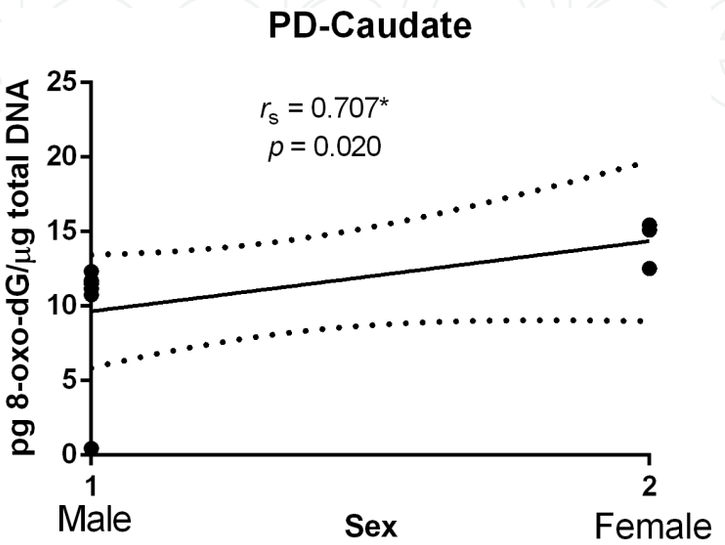


Figure 4.
Kendall's tau_b analysis of the correlation between sex and 8-oxo-dG levels in the caudate from PD brains (p = 0.020).

appearance of numerous histological features of healthy aging—gray hair, kidney disease, cataracts, osteoporosis, neuronal atrophy, and muscle atrophy. A classic mouse species survive a maximum life span of 2–4 years, whereas humans can live up to 122 years [45]. Body mass can account for approximately 60% of the mammalian life span variance, while another 40% is attributed to other factors. The mitochondrial electron transport chain yields superoxide, a reactive form of oxygen, which can damage proteins, lipids, and DNA. Superoxide generates immediately into hydrogen peroxide, promoting several forms of oxidative damage. Animals engineered to have reduced rates of oxidative lesions, make efforts to exhibit average life spans [46], which provides insights into the significant negative correlation between life span and 8-oxo-dG levels in the putamen of healthy aging groups (**Figure 5**). It seems conceivable that transcription-associated DNA damage is critically involved in the aging process of mammals.

The reverse is precisely the PDD cases, as shown in **Figure 6**, there is a significantly positive correlation between life span and 8-oxo-dG levels in the caudate of PDD patients. The result supporting a role for ROS in regulating the rate of aging was characterized as "at best equivocal" in a published comprehensive review of aging in the mouse [47], which can be explained as ROS increases life span by stimulating protective stress responses [48].

On the other side, quite a few repair enzymes recognize and remove many types of DNA damage from the genome, and failure of these mechanisms can lead to the accumulation of damage in the neurodegenerative diseases. Failure to repair DNA, in reverse, may cause the synthesis of defective proteins, which definitely will repair DNA less efficiently [49].

Genome-wide association studies (GWAS) of Huntington's disease (HD) have focused on genes associated with DNA damage repair mechanisms as modifiers of age at onset, defining an age-related mechanism shared in other hypotheses of neurodegeneration. Many ages at onset in neurodegenerative diseases are clarified to be caused by mutations in bona fide DNA repair factors—tyrosyl DNA-phosphodiesterase 1 (TDP1), aprataxin (APTX), and polynucleotide kinase/phosphatase (PNKP) [50]. Getting the picture of DNA repair defects in neurodegenerative diseases will shed light on why they affect the age at onset and the disease severity in HD.

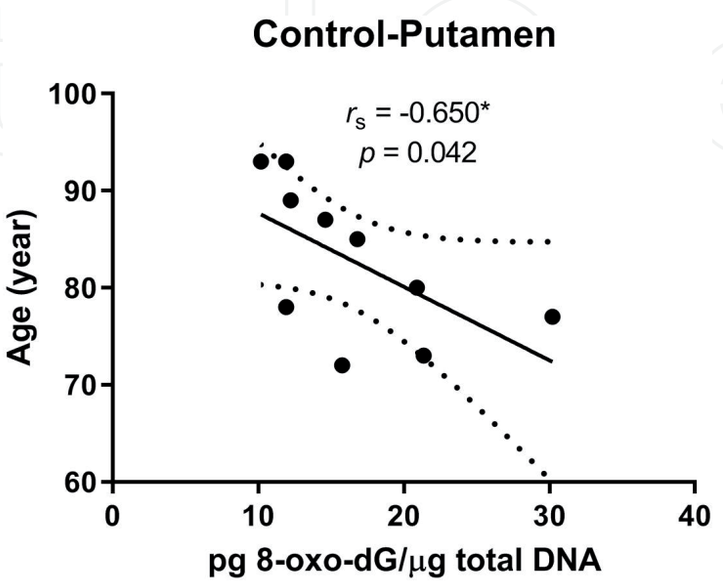


Figure 5.
Correlation between life span and 8-oxo-dG concentration in the putamen from the control brains (r_s = −0.650, p = 0.042). Rs, the Spearman's rank correlation coefficient.

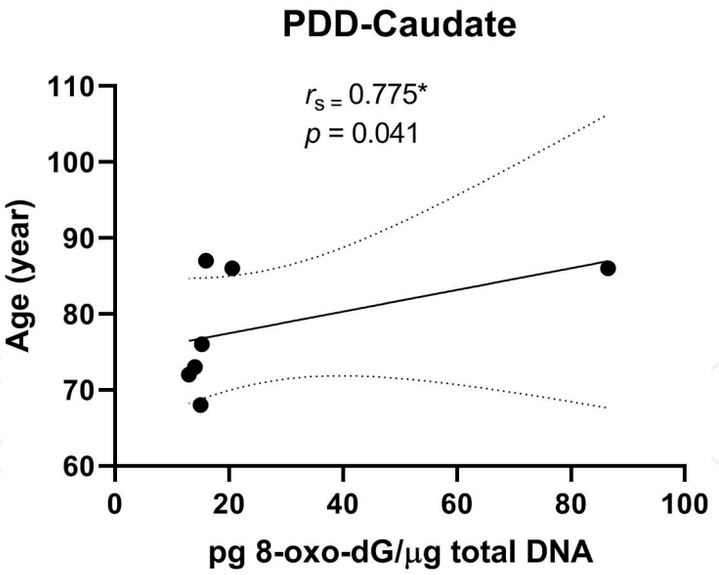


Figure 6.
Correlation between life span and 8-oxo-dG concentration in the caudate from the PDD brains (r_s = 0.775, p = 0.041). Rs, the Spearman's rank correlation coefficient.

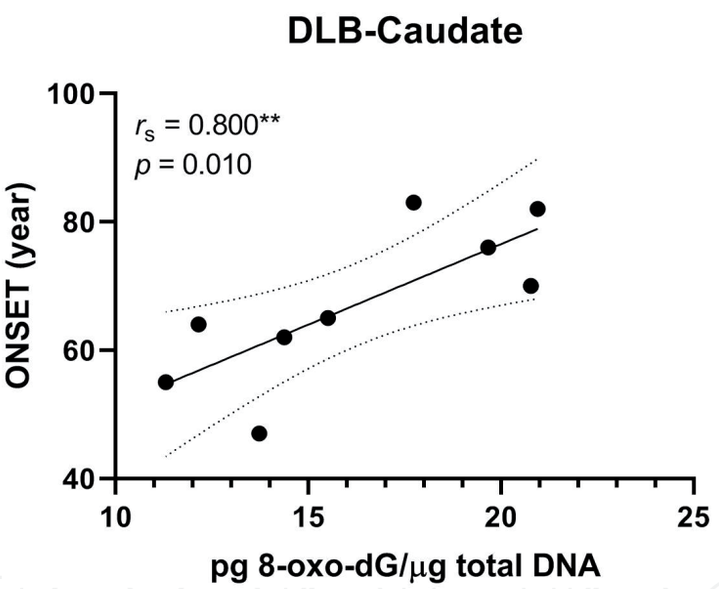


Figure 7.
Correlation between age at onset and 8-oxo-dG concentration in the caudate from the DLB brains (r_s = 0.800, p = 0.010). r_s, the Spearman's rank correlation coefficient.

An exomic sequencing study in a rare age-related ataxia oculomotor apraxia (AOA) identified mutations in the DNA repair scaffold gene *XRCC1*, the knock-out of *XRRCC1* resulted in hyper-PARlation, and genetic ablation of PARP1 prevent disease onset in an AOA-XRCC1 mouse model [51]. N6-furfuryladenine (N6FFA or kinetin)—a natural human metabolite of the DNA repairing ROS damaged adenosine—was protective against neurodegeneration in HD and PD models. The discovery of N6FFA efficacy in HD and PD models indicates a critical signaling pathway between DNA damage and mitochondria, where messed branches of this pathway may lead to different diseases in the brain, with similarities of late age onset [52]. As shown in **Figure** 7, the significantly positive correlation between age at onset and 8-oxo-dG levels in the caudate of the DLB patients, probably indicating that the DNA repair pathway, as genetic modifiers, determines the age at onset. 8-oxo-dG mainly promotes the transversion from GC to TA, GC to AT, or GC to CG, and this

is an important mechanism of ROS-induced mutation [53]. The study examined the DNA-repair capacities of basal cell carcinoma (BCC) skin cancer patients and revealed that the age at the first onset of BCC positively correlated with DNA repair, suggesting that the earlier the age of onset, the lower was their DNA repair [54].

5. Conclusion

DNA damage might progressively alter chromatin conformation and, thereby, gene expression types with age. Oxidative damage to nucleic acid is altered in midbrain structures of PD, DLB, and other neurodegenerative disease patients, consequently, inhibiting mitochondrial function. Mitochondrial dysfunction may play a vital role in the pathogenesis of neurodegeneration. What is more, there is a chicken and egg paradox in the studies trying to correlate neuronal degeneration with the signs of DNA damage.

Acknowledgements

This chapter is funded by NIH R01 NS092865. We are grateful to all participants and their families for their commitment and dedication to advance research of diagnosis and treatment for PD and AD as well as to the Knight-ADRC and MDC research staff for their contributions. We thank Dr. Nigel Cairns, Ms. Erin E. Franklin, and Mr. Michael Baxter for coordination of the tissue preparation and expert technical assistance. We also thank Mr. William Knight for editorial assistance.

Conflict of interest

The authors declare no conflicts of interest.

Other declarations

The research in this chapter was approved by the Charles F. and Joanne Knight Alzheimer disease Research Center (Knight ADRC) and Movement Disorders Center (MDC) Leadership Committees (Ethics approval reference number: T1705).

Abbreviations

ROS	reactive oxygen species
8-oxo-dG	8-oxo-7,8-dihydro-2′-deoxyguanosine
8-oxo-G	8-oxo-7,8-dihydroguanosine
PD	Parkinson disease
DLB	dementia with Lewy bodies
AD	Alzheimer disease
VMAT2	vesicular monoamine transporter 2
SRY	sex-determining region of the Y chromosome
BER	base excision repair
ALS	amyotrophic lateral sclerosis
DSBs	double-strand breaks
Aβ	β-amyloid

NFTs	neurofibrillary tangles
PDD	Parkinson disease dementia
LBD	Lewy body disease
ADHD	attention-deficit hyperactivity disorder
SNc	substantia nigra pars compact
6-OHDA	6-hydroxydopamine
GWAS	genome-wide association studies
HD	Huntington's disease
TDP1	tyrosyl DNA-phosphodiesterase 1
APTX	aprataxin
PNKP	polynucleotide kinase/phosphatase
AOA	ataxia oculomotor apraxia
N6FFA or kinetin	N6-furfuryladenine

Author details

Huifangjie Li and Jinbin Xu*
Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, MO, United States

*Address all correspondence to: jinbinxu@wustl.edu

References

[1] Guo C, Ding P, Xie C, Ye C, Ye M, Pan C, et al. Potential application of the oxidative nucleic acid damage biomarkers in detection of diseases. Oncotarget. 2017;**8**(43):75767-75777

[2] Narciso L, Parlanti E, Racaniello M, Simonelli V, Cardinale A, Merlo D, et al. The response to oxidative DNA damage in neurons: Mechanisms and disease. Neural Plasticity. 2016;**2016**:3619274

[3] Iyama T, Wilson DM III. DNA repair mechanisms in dividing and non-dividing cells. DNA Repair (Amst). 2013;**12**(8):620-636

[4] Adamec E, Vonsattel JP, Nixon RA. DNA strand breaks in Alzheimer's disease. Brain Research. 1999;**849**(1-2):67-77

[5] Jacobsen E, Beach T, Shen Y, Li R, Chang Y. Deficiency of the Mre11 DNA repair complex in Alzheimer's disease brains. Brain Research. Molecular Brain Research. 2004;**128**(1):1-7

[6] Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK, Perry RH, et al. High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. Nature Genetics. 2006;**38**(5):515-517

[7] Kraytsberg Y, Kudryavtseva E, McKee AC, Geula C, Kowall NW, Khrapko K. Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. Nature Genetics. 2006;**38**(5):518-520

[8] Pickrell AM, Pinto M, Hida A, Moraes CT. Striatal dysfunctions associated with mitochondrial DNA damage in dopaminergic neurons in a mouse model of Parkinson's disease. The Journal of Neuroscience. 2011;**31**(48):17649-17658

[9] Giannoccaro MP, La Morgia C, Rizzo G, Carelli V. Mitochondrial DNA and primary mitochondrial dysfunction in Parkinson's disease. Movement Disorders. 2017;**32**(3):346-363

[10] Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, et al. Oxidative damage is the earliest event in Alzheimer disease. Journal of Neuropathology and Experimental Neurology. 2001;**60**(8):759-767

[11] Zhang J, Perry G, Smith MA, Robertson D, Olson SJ, Graham DG, et al. Parkinson's disease is associated with oxidative damage to cytoplasmic DNA and RNA in substantia nigra neurons. The American Journal of Pathology. 1999;**154**(5):1423-1429

[12] Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: Diagnosis, treatment, molecular pathology, and biomarkers. Neurology. 2007;**68**(11):812-819

[13] Draganski B, Kherif F, Klöppel S, Cook PA, Alexander DC, Parker GJ, et al. Evidence for segregated and integrative connectivity patterns in the human basal ganglia. The Journal of Neuroscience. 2008;**28**(28):7143-7152

[14] Seger CA, Cincotta CM. The roles of the caudate nucleus in human classification learning. The Journal of Neuroscience. 2005;**25**(11):2941-2951

[15] Del Campo N, Payoux P, Djilali A, Delrieu J, Hoogendijk EO, Rolland Y, et al. Relationship of regional brain β-amyloid to gait speed. Neurology. 2016;**86**(1):36-43

[16] Mytilineou C, Han SK, Cohen G. Toxic and protective effects of L-dopa on mesencephalic cell cultures. Journal of Neurochemistry. 1993;**61**(4):1470-1478

[17] Kong Q, Lin CL. Oxidative damage to RNA: Mechanisms, consequences, and diseases. Cellular and Molecular Life Sciences. 2010;**67**(11):1817-1829

[18] Hall FS, Itokawa K, Schmitt A, Moessner R, Sora I, Lesch KP, et al. Decreased vesicular monoamine transporter 2 (VMAT2) and dopamine transporter (DAT) function in knockout mice affects aging of dopaminergic systems. Neuropharmacology. 2014;**76**(Pt A(0 0)):146-155

[19] Czech DP, Lee J, Correia J, Loke H, Möller EK, Harley VR. Transient neuroprotection by SRY upregulation in dopamine cells following injury in males. Endocrinology. 2014;**155**(7):2602-2612

[20] Casarett GW. Similarities and contrasts between radiation and time pathology. Advances in Gerontological Research. 1964;**18**:109-163

[21] Li H, Yang P, Knight W, Guo Y, Perlmutter JS, Benzinger TLS, et al. The interactions of dopamine and oxidative damage in the striatum of patients with neurodegenerative diseases. Journal of Neurochemistry. 2020;**152**(2):235-251

[22] Gmitterová K, Gawinecka J, Heinemann U, Valkovič P, Zerr I. DNA versus RNA oxidation in Parkinson's disease: Which is more important? Neuroscience Letters. 2018;**662**:22-28

[23] Nunomura A, Perry G, Pappolla MA, Friedland RP, Hirai K, Chiba S, et al. Neuronal oxidative stress precedes amyloid-beta deposition in Down syndrome. Journal of Neuropathology and Experimental Neurology. 2000;**59**(11):1011-1017

[24] Kikuchi A, Takeda A, Onodera H, Kimpara T, Hisanaga K, Sato N, et al. Systemic increase of oxidative nucleic acid damage in Parkinson's disease and multiple system atrophy. Neurobiology of Disease. 2002;**9**(2):244-248

[25] Chen CM, Liu JL, Wu YR, Chen YC, Cheng HS, Cheng ML, et al. Increased oxidative damage in peripheral blood correlates with severity of Parkinson's disease. Neurobiology of Disease. 2009;**33**(3):429-435

[26] Abe T, Isobe C, Murata T, Sato C, Tohgi H. Alteration of 8-hydroxyguanosine concentrations in the cerebrospinal fluid and serum from patients with Parkinson's disease. Neuroscience Letters. 2003;**336**(2):105-108

[27] Kikuchi Y, Yasuhara T, Agari T, Kondo A, Kuramoto S, Kameda M, et al. Urinary 8-OHdG elevations in a partial lesion rat model of Parkinson's disease correlate with behavioral symptoms and nigrostriatal dopaminergic depletion. Journal of Cellular Physiology. 2011;**226**(5):1390-1398

[28] Youdim MBH. Monoamine oxidase inhibitors, and iron chelators in depressive illness and neurodegenerative diseases. Journal of Neural Transmission (Vienna). 2018;**125**(11):1719-1733

[29] Winterbourn CC. Toxicity of iron and hydrogen peroxide: The Fenton reaction. Toxicology Letters. 1995;**82-83**:969-974

[30] Spencer WA, Jeyabalan J, Kichambre S, Gupta RC. Oxidatively generated DNA damage after Cu(II) catalysis of dopamine and related catecholamine neurotransmitters and neurotoxins: Role of reactive oxygen species. Free Radical Biology & Medicine. 2011;**50**(1):139-147

[31] Linert W, Jameson GN. Redox reactions of neurotransmitters possibly involved in the progression of Parkinson's disease. Journal of Inorganic Biochemistry. 2000;**79**(1-4):319-326

[32] Gołembiowska K, Dziubina A. The effect of adenosine A(2A) receptor antagonists on hydroxyl radical,

dopamine, and glutamate in the striatum of rats with altered function of VMAT2. Neurotoxicity Research. 2012;**22**(2):150-157

[33] Carlsson A, Lindqvist M, MagnussonT.3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. Nature. 1957;**180**(4596):1200

[34] Gao R, Zhang G, Chen X, Yang A, Smith G, Wong DF, et al. CSF biomarkers and its associations with 18F-AV133 cerebral VMAT2 binding in Parkinson's disease - A preliminary report. PLoS One. 2016;**11**(10):e0164762

[35] Cahill L. Why sex matters for neuroscience. Nature Reviews. Neuroscience. 2006;**7**(6):477-484

[36] Bao AM, Swaab DF. Sex differences in the brain, behavior, and neuropsychiatric disorders. The Neuroscientist. 2010;**16**(5):550-565

[37] Czech DP, Lee J, Sim H, Parish CL, Vilain E, Harley VR. The human testis-determining factor SRY localizes in midbrain dopamine neurons and regulates multiple components of catecholamine synthesis and metabolism. Journal of Neurochemistry. 2012;**122**(2):260-271

[38] Dewing P, Chiang CW, Sinchak K, Sim H, Fernagut PO, Kelly S, et al. Direct regulation of adult brain function by the male-specific factor SRY. Current Biology. 2006;**16**(4):415-420

[39] Gillies GE, McArthur S. Estrogen actions in the brain and the basis for differential action in men and women: A case for sex-specific medicines. Pharmacological Reviews. 2010;**62**(2):155-198

[40] Arnold AP. Sex chromosomes and brain gender. Nature Reviews. Neuroscience. 2004;**5**(9):701-708

[41] Carruth LL, Reisert I, Arnold AP. Sex chromosome genes directly affect brain sexual differentiation. Nature Neuroscience. 2002;**5**(10):933-934

[42] Lee J, Harley VR. The male fight-flight response: A result of SRY regulation of catecholamines? BioEssays. 2012;**34**(6):454-457

[43] Bourque M, Morissette M, Di Paolo T. Repurposing sex steroids and related drugs as potential treatment for Parkinson's disease. Neuropharmacology. 2019;**147**:37-54

[44] Lee J, Pinares-Garcia P, Loke H, Ham S, Vilain E, Harley VR. Sex-specific neuroprotection by inhibition of the Y-chromosome gene, SRY, in experimental Parkinson's disease. Proceedings of the National Academy of Sciences of the United States of America. 2019;**116**(33):16577-16582

[45] Tuchweber B, Salas M. Experimental pathology of aging. Methods and Achievements in Experimental Pathology. 1975;**7**:167-226

[46] Callegari AJ. Does transcription-associated DNA damage limit lifespan? DNA Repair (Amst). 2016;**41**:1-7

[47] Liao CY, Kennedy BK. Mouse models and aging: Longevity and progeria. Current Topics in Developmental Biology. 2014;**109**:249-285

[48] Longo VD, Shadel GS, Kaeberlein M, Kennedy B. Replicative and chronological aging in *Saccharomyces cerevisiae*. Cell Metabolism. 2012;**16**(1):18-31

[49] Clingen PH, Lowe JE, Green MH. Measurement of DNA damage and repair capacity as a function of age using the comet assay. Methods in Molecular Medicine. 2000;**38**:143-157

[50] Jiang B, Glover JN, Weinfeld M. Neurological disorders associated with DNA strand-break processing enzymes. Mechanisms of Ageing and Development. 2017;**161**(Pt A):130-140

[51] Hoch NC, Hanzlikova H, Rulten SL, Tétreault M, Komulainen E, Ju L, et al. Rey SA and others. XRCC1 mutation is associated with PARP1 hyperactivation and cerebellar ataxia. Nature. 2017;**541**(7635):87-91

[52] Maiuri T, Bowie LE, Truant R. DNA repair signaling of Huntingtin: The next link between late-onset neurodegenerative disease and oxidative DNA damage. DNA and Cell Biology. 2019;**38**(1):1-6

[53] Kasai H. Analysis of a form of oxidative DNA damage, 8-hydroxy-2′-deoxyguanosine, as a marker of cellular oxidative stress during carcinogenesis. Mutation Research. 1997;**387**(3):147-163

[54] Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L. DNA repair and aging in basal cell carcinoma: A molecular epidemiology study. Proceedings of the National Academy of Sciences of the United States of America. 1993;**90**(4):1614-1618