Namrata Mittra

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Academics Qualifications

- 2013-2020: Ph.D. (*Biotechnology*) from **CSIR-IITR** (Under AcSIR), Delhi, India
- 2010-2012: M.Sc in Biotechnology, **gold medalist** from Integral University, Lucknow, India
- 2007-2010: B.Sc (*Hons*.) in Biotechnology, **gold medalist** from Integral University, Lucknow, India

Research Experience (5years)

Worked at CSIR-IITR as a Ph.D research scholar on **"Effect of developmental exposure to zinc or paraquat on adulthood re-exposure: relevance to parkinson's disease"** under the guidance of **Dr. Chetna Singh** (Senior Principal Scientist), Developmental Toxicology Laboratory.

Research Highlights:

- Postnatal Zn/PQ exposure + adult re-exposure on dopaminergic neurodegenerative aspect
- Mitochondrial dysfunction and inflammation involved in Zn/PQ exposed during postnatal period followed by adult re-exposure
- A study on the apoptotic mechanism

Technical skills/ Activities:

- Animal (Rat) handling, intraperitoneal injection (i.p.)

- *Biochemical and Molecular techniques*
- *RNA Isolation*
- *Polymerase chain reaction (PCR)*
- *Immunohistochemistry*
- *Immunoflorescence*
- *Western blotting*
- *High performance liquid chromatography (HPLC)*
- *Liquid chromatography-Mass Spectrometry (LC-MS)*
- *Neuromotor activity tests:*

- *Spontaneous Locomotor activity*
- *Rotarod performance test*

Honors/Awards

- Received **International Society of Neurochemistry** (**ISN) Travel award** in 2017 to attend ISN-ESN conference in Paris, France.

- Qualified **Department of science and technology-Innovation in science pursuit for inspired research (DST-INSPIRE) Fellowship for doctoral research (Ph.D.)** in 2013

- 2015-2019: Award of **Senior Research Fellowship** by Department of science and technology-Innovation in science pursuit for inspired research **(DST-INSPIRE)**, India.
- 2013-2015: Award of **Junior Research Fellowship** by Department of science and technology-Innovation in science pursuit for inspired research **(DST INSPIRE)**, India.
- Received **GOLD MEDAL** for 1st rank holder in M.Sc. Biotechnology at University level in 2012
- Received **GOLD MEDAL** for 1st rank holder in department of Biotechnology, Integral University in 2012
- Received **GOLD MEDAL** for 1st rank holder in B.Sc. Biotechnology at University level in 2010
- Received **GOLD MEDAL** for 1st rank holder in department of Biotechnology, Integral University in 2010

PROFESSIONAL MEMBERSHIP:

- Member of **International Society of Neurochemistry (ISN)** from 2017

Poster presented at National/International Conferences:

- ***Namrata Mittra,*** Amit Kumar Chauhan and Chetna Singh. Postnatal exposure augments neurotoxicity of zinc/paraquat exposed adult rats on oxidative stress, monoamine transporters and apoptosis. Presented in binneal meeting of **International Society of Neurochemistry (ISN) and the European Society for Neurochemistry (ESN),** August 20-24, 2017 at Paris, France.
- ***Namrata Mittra,*** Amit Kumar Chauhan and Chetna Singh. Role of mitochondrial dysfunction in Zinc induced nigrostratal dopaminergic neurodegeneration. Presented in IIIrd **International Toxicology Conclave (ITC)**, November 5-6, 2017, at CSIR-IITR, Lucknow, India.
- ***Namrata Mittra,*** Amit Kumar Chauhan and Chetna Singh. Developmental exposure to Zn/PQ enhances the susceptibility to dopaminergic neurodegeneration on adulthood re-exposure. Presented in XXXIV annual meeting of ***Indian academy of neurosciences* (*IAN*),** October 19th to 21st 2016 at National Brain Research Centre (NBRC), Manesar, Gurgaon, India.

Abstract published at National/International journal:

- **Namrata Mittra,** Amit Kumar Chauhan and Chetna Singh. (2017). Postnatal exposure augments neurotoxicity of zinc/paraquat exposed adult rats on oxidative stress, monoamine transporters and apoptosis. International Society for Neurochemistry, J. Neurochem. 142 (Suppl. 1), 165—259. WTH07-31
- **Namrata Mittra,** Amit Kumar Chauhan and Chetna Singh. (2016). Developmental exposure to zinc/paraquat enhances the susceptibility to dopaminergic neurodegeneration on adulthood re-exposure. 34th Annual Meeting of India Academy of Neurosciences “Molecules to Mind”. 240.

Research papers published:

- **Mittra N**, Chauhan AK, Singh G, Patel DK, Singh C (2020). Postnatal zinc or paraquat administration increases paraquat or zinc-induced loss of dopaminergic neurons: Insight into augmented neurodegeneration. Molecular and cellular biochemistry; 467(1-2):27-43.
- Chauhan AK, **Mittra N**, Singh BK, Singh C (2019). Inhibition of glutathione S-transferase-pi triggers c-jun N-terminal kinase-dependent neuronal death in Zn-induced Parkinsonism. Mol Cell Biochem; 452(1-2):95-104.
- Kumar V, Singh D, Singh BK, Singh S, **Mittra N**, Jha RR, Patel DK, Singh C (2018). Alpha-synuclein aggregation, Ubiquitin proteasome system impairment, and L-Dopa response in zinc-induced Parkinsonism: resemblance to sporadic Parkinson's disease. Mol Cell Biochem; 444(1-2):149-160.
- Chauhan AK, **Mittra N**, Patel DK, Singh C (2018). Cyclooxygenase-2 Directs Microglial Activation-Mediated Inflammation and Oxidative Stress Leading to Intrinsic Apoptosis in Zn-Induced Parkinsonism. Mol Neurobiol;55(3):2162-2173
- Chauhan AK, **Mittra N**, Kumar V, Patel DK, Singh C (2016). Inflammation and B-cell Lymphoma-2 Associated X Protein Regulate Zinc-Induced Apoptotic Degeneration of Rat Nigrostriatal Dopaminergic Neurons. Mol Neurobiol; 53(8):5782-95.

References:

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Date: **10-06-2020**
Place: **Lucknow**

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LIST OF PUBLICATIONS

Molecular and Cellular Biochemistry
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Postnatal zinc or paraquat administration increases paraquat or zinc-induced loss of dopaminergic neurons: insight into augmented neurodegeneration

Namrata Mittra[1,2] · Amit Kumar Chauhan[1,2] · Garima Singh[1,2] · Devendra Kumar Patel[3] · Chetna Singh[1,2]

Received: 22 July 2019 / Accepted: 20 January 2020

Abstract

Epidemiological evidences have shown an association of exposure to pesticides or heavy metals with increased incidences of Parkinson's disease (PD) in humans. Exposure to pesticides or metals during the decisive period of the brain development increases the susceptibility of dopaminergic neurons upon re-exposure in adult rodents. However, the effect of early life exposure to pesticide on the heavy metal-induced neurodegeneration or heavy metal on pesticide-induced neurodegeneration is not yet explored. The current study explored the effect of developmental exposure to zinc (Zn), a metal or paraquat (PQ), a pesticide on the nigrostriatal dopaminergic neurons of rats challenged to Zn or PQ during adulthood. Exposure of Zn or PQ during adulthood alone exhibited marked reduction in motor activities, striatal dopamine and metabolites, gluiathione content and number of dopaminergic neurons. However, the levels of lipid peroxidation, protein carbonyls, superoxide dismutase activity, pro-inflammatory cytokines and 4-hydroxynonenal-protein adducts were increased. While the expression of vesicular monoamine transporter-2 and tyrosine hydroxylase were attenuated, dopamine transporter and microglial marker Iba-1 expression, activated microglia, nuclear factor-kappaB activation, mitochondrial cytochrome c release and caspase-3/9 activation were augmented following Zn or PQ exposure. Albeit postnatal alone exposure did not alter any of the studied parameters, the developmental administration of Zn/PQ in re-challenged adult rats produced more pronounced changes in the aforementioned variables as compared with adulthood Zn or PQ alone intoxicated animals. The results demonstrate that postnatal Zn/PQ intoxication dents the oxidative stress, inflammation, cell death and dopamine metabolism and storage regulating machineries, which speed up the toxicant-induced degeneration during adulthood.

Keywords Zinc · Paraquat · Neurodegeneration · Oxidative stress · Inflammation

Introduction

Parkinson's disease (PD) is an age-related debilitating neurological disorder characterized by symptoms depicting motor dysfunction due to marked striatal dopamine deficit, which is caused by selective loss of dopamine synthesizing neurons in the substantia nigra pars compacta (SNpc) region of the mid brain [1, 2]. PD exhibits a multi-factorial etiology resulting from a composite interplay between age, genetic predisposition and environmental factors [2, 3]. Epidemiological data have recognized exposure to pesticides and heavy metals as putative risk factors for increased incidences of PD in humans [3–6].

Paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride; PQ), a widely used bipyridyl herbicide, is a well established environmental toxin associated with dopaminergic neurodegeneration leading to PD in animal models and humans [7, 8]. PQ is a free radical generator, which itself undergoes redox cycling leading to ROS generation and subsequently oxidative stress [9]. Increased oxidative stress, mitochondrial dysfunction, microglial activation and neuroinflammation are recognized as main contributors of PQ-induced

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Inhibition of glutathione S-transferase-pi triggers c-jun N-terminal kinase-dependent neuronal death in Zn-induced Parkinsonism

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Abstract

Oxidative stress is recognized as one of the major wrongdoers in Parkinson's disease (PD) while glutathione *S*-transferase (GST), an endogenous antioxidant, protects from oxidative stress-induced neurodegeneration. Despite GST-pi (GST-π) encounters the toxic manifestations in PD, its role in zinc (Zn)-induced nigrostriatal dopaminergic neurodegeneration remains elusive. The study aimed to explore the role of GST-π in Zn-induced Parkinsonism and its underlying molecular mechanism. Male Wistar rats were treated intraperitoneally with zinc (zinc sulfate), twice a week, for 2–12 weeks. GST-π inducer, benzyl isothiocyanate (BITC) was also administered in a few sets of experiments along with respective vehicle. Catalytic activity and expression of GST-π protein, total GST activity, neurobehavioral indexes, striatal dopamine and its metabolites, nigral tyrosine hydroxylase (TH)-positive neurons and expression of TH and B-cell lymphoma-2 (Bcl-2) proteins were reduced in Zn-treated rats. Conversely, oxidative stress indicators, c-jun N-terminal kinase (JNK) activation, c-jun phosphorylation, cytochrome c release, Bcl-2-associated X protein (Bax) translocation, and procaspase 3/9 to caspase 3/9 conversion were significantly increased in Zn-exposed rats. BITC ameliorated GST-π activity/expression and normalized Zn-induced changes in neurodegenerative indicators, oxidative stress, JNK activation, c-jun phosphorylation and apoptotic indexes. The results demonstrate that Zn inhibits GST-π expression leading to increased oxidative stress and JNK activation, which induce apoptosis thereby degeneration of the nigrostriatal dopaminergic neurons.

Keywords Zinc · Nigrostriatal dopaminergic neurodegeneration · Oxidative stress · Glutathione S-transferase-pi

Introduction

Parkinson's disease (PD) is a prevalent, chronic neurological disorder resulting in motor dysfunction caused by the selective loss of the dopamine synthesizing neurons in the substantia nigra (SN) region of midbrain. A multi-factorial aetiology has been suggested with age, genetic and environmental factors as the putative perils for the onset and progression of PD [1, 2]. Meta analysis studies have revealed a strong positive correlation between the exposure to heavy metals and increased risk of PD [3, 4]. Clinical evidences documenting increased Zn levels in the substantia nigra region of brain of PD patients implicated its role in PD pathogenesis [5]. This is substantiated by experimental studies reporting Zn-induced dopaminergic neurodegeneration and PD-like features in rodents [6–9].

Increased vulnerability of dopaminergic neurons towards oxidative stress is attributed to the presence of high levels of iron (Fe^{3+}), α-synuclein, oxidized dopamine, polyunsaturated fatty acid (PUFA), and impaired calcium signaling [10]. Epidemiological evidences have established a strong association between oxidative stress and increased incidences of PD. It is supported by animal models of PD developed through toxicants exposure, which cause oxidative stress. Toxicants used for this purpose include 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxy dopamine (6-OHDA), paraquat, rotenone, iron, and zinc [9–11]. Furthermore, reduced glutathione (GSH) content, elevated lipid peroxides, reduced mitochondrial complex I

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Cyclooxygenase-2 Directs Microglial Activation-Mediated Inflammation and Oxidative Stress Leading to Intrinsic Apoptosis in Zn-Induced Parkinsonism

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Abstract Inflammation is decisive in zinc (Zn)-induced nigrostriatal dopaminergic neurodegeneration; however, the contribution of cyclooxygenase-2 (COX-2) is not yet known. The present study aimed to explore the role of COX-2 in Zn-induced Parkinsonism and its association with the microglial activation. Male Wistar rats were treated intraperitoneally (i.p.) with Zn as zinc sulphate (20 mg/kg) along with respective controls for 2–12 weeks. In a few sets, animals were also treated with/without celecoxib (CXB, 20 mg/kg, i.p.), a selective COX-2 inhibitor. Indexes of the nigrostriatal neurodegeneration, oxidative stress, inflammation and apoptosis were measured in the animals/nigrostriatal tissue. Zn induced time-dependent increase in the expression of COX-2 while COX-1 expression was unaltered. Zn reduced the neurobehavioral activities, striatal dopamine content, tyrosine hydroxylase (TH) expression and number of dopaminergic neurons. While oxidative stress, microglial activation; expression of microglial cell surface marker-CD11b; cytochrome c release; caspase-9/3 activation; level of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6 and Bcl-2-associated protein x (Bax) translocation from the cytosol to mitochondria were induced in the Zn-treated group, expression of B-cell lymphoma-2 (Bcl-2) was found to be reduced. CXB significantly attenuated Zn-induced increase in COX-2 expression and restored TH-expression, dopamine content, level of inflammatory cytokines and neurobehavioral indexes towards normalcy. Moreover, CXB also attenuated Zn-induced increase in microglial activation, oxidative stress and apoptotic markers towards normal levels. Results of the study thus demonstrate that COX-2 induces microglial activation that provokes the release of inflammatory mediators, which in turn augments oxidative stress and intrinsic apoptosis leading to dopaminergic neurodegeneration in Zn-induced Parkinsonism.

Keywords Zinc · Oxidative stress · Nigrostriatal dopaminergic neurodegeneration · Cyclooxygenase-2 · Neuroinflammation

Introduction

Parkinson's disease (PD) is a mysterious, chronic and progressive neurodegenerative disorder of the nigrostriatal dopaminergic pathway leading to motor disability and characterized by anatomical hallmarks like striatal dopamine depletion and Lewy body formation [1–3]. Despite extensive strategies adopted to explore the molecular explanations of the disease, aetiology remains elusive and ageing, genetic predisposition and environmental factors have been projected as the major perils [4]. Exposure to pesticides and heavy metals has been found to exhibit considerable correlation with high disease risk [5–7]. Presence of elevated zinc (Zn) content in the substantia nigra of PD patients [8] and occurrence of selective nigrostriatal dopaminergic neurodegeneration leading to PD phenotype in the experimental rodents following systemic Zn

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Alpha-synuclein aggregation, Ubiquitin proteasome system impairment, and L-Dopa response in zinc-induced Parkinsonism: resemblance to sporadic Parkinson's disease

Vinod Kumar[1,2] · Deepali Singh[1,2] · Brajesh Kumar Singh[1] · Shweta Singh[1] · Namrata Mittra[1,2] · Rakesh Roshan Jha[3] · Devendra Kumar Patel[3] · Chetna Singh[1,2]

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Abstract
Alpha-synuclein (α-synuclein) aggregation and impairment of the Ubiquitin proteasome system (UPS) are implicated in Parkinson's disease (PD) pathogenesis. While zinc (Zn) induces dopaminergic neurodegeneration resulting in PD phenotype, its effect on protein aggregation and UPS has not yet been deciphered. The current study investigated the role of α-synuclein aggregation and UPS in Zn-induced Parkinsonism. Additionally, levodopa (L-Dopa) response was assessed in Zn-induced Parkinsonian model to establish its closeness with idiopathic PD. Male Wistar rats were treated with zinc sulfate (Zn; 20 mg/kg; i.p.) twice weekly for 12 weeks along with respective controls. In few subsets, animals were subsequently treated with L-Dopa for 21 consecutive days following Zn exposure. A significant increase in total and free Zn content was observed in the substantia nigra of the brain of exposed groups. Zn treatment caused neurobehavioral anomalies, striatal dopamine decline, and dopaminergic neuronal cell loss accompanied with a marked increase in α-synuclein expression/aggregation and Ubiquitin-conjugated protein levels in the exposed groups. Zn exposure substantially reduced UPS-associated trypsin-like, chymotrypsin-like, and caspase-like activities along with the expression of SUG1 and β-5 subunits of UPS in the nigrostriatal tissues of exposed groups. L-Dopa treatment rescued from Zn-induced neurobehavioral deficits and restored dopamine levels towards normalcy; however, Zn-induced dopaminergic neuronal loss, reduction in tyrosine hydroxylase expression, and increase in oxidative stress were unaffected. The results suggest that Zn caused UPS impairment, resulting in α-synuclein aggregation subsequently leading to dopaminergic neurodegeneration, and that Zn-induced Parkinsonism exhibited positive L-Dopa response similar to sporadic PD.

Keywords Zinc · α-Synuclein aggregation · Ubiquitin proteasome system · Parkinson's disease · L-Dopa

Introduction

Parkinson's disease (PD) is a debilitating progressive movement disorder resulting from declined striatal dopamine levels due to selective dopaminergic neuronal loss in the substantia nigra pars compacta (SNpc) of ventral midbrain. Cardinal visual symptoms of PD include resting tremor, muscular rigidity, bradykinesia, and postural instability, while the presence of Lewy bodies and Lewy neurites in surviving dopaminergic neurons is considered as the anatomical hallmark of the sporadic PD [1]. Although the exact cause and mechanisms responsible for PD onset are not yet completely understood, clinical and experimental evidences suggest contribution of age and environmental and genetic factors in the manifestations of PD [2, 3]. Postmortem studies showing increased zinc (Zn) accumulation in dopaminergic

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Inflammation and B-cell Lymphoma-2 Associated X Protein Regulate Zinc-Induced Apoptotic Degeneration of Rat Nigrostriatal Dopaminergic Neurons

Amit Kumar Chauhan[1,2] · Namrata Mittra[1,2] · Vinod Kumar[1,2] · Devendra Kumar Patel[3] · Chetna Singh[1,2]

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Abstract Clinical evidences showing zinc (Zn) accumulation in the post-mortem brain of Parkinson's disease (PD) patients and experimental studies on rodents chronically exposed to Zn suggested its role in PD. While oxidative stress is implicated in Zn-induced neurodegeneration, roles of inflammation and apoptosis in degeneration of the nigrostriatal dopaminergic neurons have yet been elusive. The present study investigated the contribution of the nuclear factor kappa B (NF-κB), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and B-cell lymphoma 2 (Bcl-2) family proteins in Zn-induced Parkinsonism. Male Wistar rats were treated with/without zinc sulfate (Zn; 20 mg/kg, intraperitoneally), twice a week, for 2–12 weeks. In a few sets, animals were treated intraperitoneally with a NF-κB inhibitor, pyrrolidine dithiocarbamate (PDTC; 100 mg/kg), a TNF-α inhibitor, pentoxyfylline (PTX; 50 mg/kg), and an anti-inflammatory agent, dexamethasone (DEX; 5 mg/kg), prior to Zn exposure along with respective controls. Zn caused neurobehavioral impairments and reduction in dopamine and its metabolites, tyrosine hydroxylase (TH)-positive neurons, catalase activity, and expression of TH, Bcl-2, and NOXA. On the contrary, Zn augmented lipid peroxidation, activity of superoxide dismutase, expression of TNF-α, IL-1β, Bcl-xl, and p53-upregulated modulator of apoptosis (PUMA), and translocation of NF-κB and Bax from the cytosol to the nucleus and mitochondria, respectively, with concomitant increase in the mitochondrial cytochrome *c* release and activation of procaspase-3 and -9. Pre-treatment with PTX, DEX, or PDTC invariably ameliorated Zn-induced changes in behavioral and neurodegenerative indexes, inflammatory mediators, and apoptosis. Results demonstrate that inflammation regulates Bax expression that subsequently contributes to the nigrostriatal dopaminergic neurodegeneration.

Keywords Zinc · Inflammation · Oxidative stress · Neurodegeneration · Apoptosis

Introduction

Parkinson's disease (PD) is a widespread progressive degenerative movement disorder of the central nervous system. It has a multi-factorial etiology with age and genetic and environmental factors as the major putative risk factors, which lead to the selective and progressive death of dopamine producing neurons in the substantia nigra pars compacta (SNpc) region of the midbrain [1]. Pesticides and heavy metals comprise the main environmental factors associated with increased incidences of PD [2, 3]. The role of Zn in PD pathogenesis, suggested by the increased accumulation of Zn in the substantia nigra region of the brain of PD patients [4], was supported by the animal studies documenting dopaminergic neurodegeneration in rodents chronically exposed to Zn resulting in PD phenotype [5–7]. Oxidative stress is established as a key player in Zn-induced dopaminergic neurodegeneration; however,

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