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Prenatal exposure to nickel triggers redox imbalance and histological alterations in the brain of infant and adolescent rats

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Abstract
Nickel has been linked to various neurodevelopmental deficits. Therefore, this study aims to unravel the mechanism through which prenatal exposure Ni may trigger neurodevelopmental disruptions in postnatal life. Ten pregnant Wistar rats were divided into two groups; control and Ni-treated groups. The control group was administered normal saline while the Ni group was treated with 20 mg/kg body weight of $NiCl_2$ from gestational day 7 – 21. After parturition, pups were sacrificed on postnatal days 21 and 42. Their brains were excised for biochemical estimation of malondialdehyde, nitric oxide and glutathione as well as histological analysis of the hippocampal CA3. Our findings revealed elevated malondialdehyde and NO activity with depleted GSH level in the brains prenatally exposed to Ni. Histological distortions from oxidative damage were prominent in this group. We concluded that prenatal exposure to Ni could induce neurodevelopmental abnormality via oxidative stress in the rat brain to provoke neuronal injury.
Key words: Nickel, oxidative stress, cell death, neurodevelopment

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INTRODUCTION

In recent years, it's generally known that early exposure to a range of environmental contaminants is a major risk factor for many disorders in later life. Early life is commonly understood to include both the prenatal phase, in which the fetus is exposed to many environmental elements, and the postnatal period; together posing a critical window for vulnerability to potential health deficits. The most widely recognized theory holds that exposure to various stimuli during the perinatal and/or postnatal phases of life impacts the development of target organs, upsetting homeostasis and raising the risk of diseases in adulthood (Antonelli et al., 2017).

The most notable consequence of our society's evolution is likely the heavy metal-related pollution of soil, water, and air. Heavy metals are specifically considered neurodevelopmental toxins because they can cause fetal damages that result in neurological defects, developmental delays, learning disabilities, and behavioral abnormalities (Gorini et al., 2014). Metals are typical chemical substances that are engaged in a wide range of biological activities. Although they are essential to life, excessive exposure can have detrimental neurological effects that are worrisome for the health of the general public. Overexposure to metals has been linked to aberrant brain development, significantly raising the risk of neurological problems during developing stages and/or in later life (Kim et al., 2022). The placenta may serve as a conduit for fetal exposure to heavy metals, which can also be found in the umbilical cord and amniotic fluid (McDermott et al., 2015). According to Caserta et al. (2013), there is evidence in both human and animal literature that the placenta is porous and that this increases the vulnerability of the fetus to exposure. Exposure has been shown to cause DNA damage, oxidative cell stress, damage to the neurological system, problems with the metabolism of glucose, and disruption of the endocrine system (Gollenberg et al., 2010; Grandjean & Landrigan, 2006; Gundacker et al., 2010; McDermott et al., 2015)

Nickel (Ni) is a metal to which humans are frequently exposed due to its great natural abundance. Given that Ni is so abundant in food, it is often impossible for the human body to become nickel deficient; rather, it is difficult to maintain a diet lacking in nickel (Begum et al., 2022). A wide variety of foods contain nickel, including: Hazelnuts; cocoa and dark chocolate; fruits (almonds, dates, figs, pineapple, plums, raspberries); grains (bran, buckwheat, millet, whole grain bread, oats, brown rice, sesame seeds, sunflower seeds); seafood (shrimps, mussels, oysters, crab, salmon); vegetables (beans, savoy cabbage, leeks, lettuce, lentils, peas, spinach, cabbage), tea from drinks dispensers; soya and soya products; peanuts; licorice; baking powder (Begum et al., 2022; Genchi et al., 2020). The plant and soil nickel content both affect how much nickel is present in a given food. This is mainly because plants and seafood, including fish, have become contaminated due to the elevated concentration of nickel in the soil and water bodies, particularly in industrial areas (Klein & Costa, 2022). As a result, oral consumption of these tainted plant and animal products exposes humans to Ni (Cempel & Nikel, 2006). Similarly, cooking tools (such as roasting pans and oven pans) significantly increased the amount of nickel in cooked food. According to Calogiuri et al. (2016), nickel contents in acidic foods increase when stainless-steel pans are used. Other sources of Ni exposure include occupational exposure. In occupational settings, exposure to nickel and nickel compounds occurs primarily during nickel refining, electroplating, and welding (Zhao et al., 2009). Additionally,

several industrial processes such as metal-cutting and metal-forming activities, metal spraying, sintering, chemical production, manufacturing of glass, batteries and accumulators, have all been shown to expose workers to median nickel concentrations greater than 10 μg/m^3(Behrens et al., 2023).

Overexposure to nickel causes toxicities in various organs, including the brain, irrespective of the source of exposure (Ijomone et al., 2020a; Ijomone et al., 2018). Oxidative stress is one of the numerous processes linked to nickel-mediated neurotoxicity; it can harm tissue, including the central nervous system (CNS), resulting in altered physicochemical characteristics of cell membranes and impaired neuronal function, which can ultimately impair essential functions and total brain activity (Das et al., 2008, Lamtai et al., 2018, Rao et al., 2009). Numerous studies have focused on the Ni-induced toxicity in the brains of adult rats. Obstetricians have long been concerned about the fetus's susceptibility to toxic exposure. Exposure to certain biologic agents and/or chemicals has been linked to both structural and neurodevelopmental abnormalities (McDermott et al., 2015). Since Ni is implicated in the pathogenesis of neurodevelopmental abnormalities, it is pertinent to investigate the mechanism through which Ni could induce neurodevelopmental disruptions; hence, this study investigated the role of prenatal exposure to nickel in the brain of developing Wistar rats.

2.0 METHODS

2.1 Chemicals and Reagents

Nickel chloride (NiCl2) as nickel (II) chloride hexahydrate (NiCl2.6H20); nicotinamide adenine dinucleotide phosphate (NADP); epinephrine; glutathione (GSH); 5, 5-dithio-bis-2-nitrobenzoic acid; hydrogen peroxide; thiobarbituric acid (TBA); and 1-chloro-2, 4-dinitrobenzoic acids were purchased from Sigma-Aldrich Chemical CO (St. Louis, MO, USA). All other reagents were of analytical grade.

2.2 Animal Care

A total of 10 female rats and 5 male rats weighing 170 – 220 g were purchased and housed in the animal holding of the Department of Human Anatomy, Federal University of Technology Akure, Nigeria. The animals were kept in individual cages and had unlimited access to water and standard laboratory rodent feed.

2.3 Mating and Grouping of Animals

Before the animals were allowed to mate by natural copulation, a vaginal smear test was carried out every day. Natural copulation was the method of mating. The vaginal smear method developed by Marcoides was used to verify mating (Akingbade et al., 2021; Marcondes et al., 2002). The day after mating was then considered to be the first day of pregnancy. Pregnant rats were randomly divided into two groups – a control and a treatment (Nickel) groups. The control group received normal saline while the Ni group was administered 20 mg/kg body weight.

Nickel was administered via oral gavage from gestational day 7 – 21. Dosse was based on our previous studies (Ijomone et al., 2018). After delivery, separate pups (n = 5) were evaluated on postnatal days 21 (weaned), and 42 (adolescence). Animals were sacrificed and brains were quickly excised and processed for biochemical assays and histopathological examination.

2.3 Biochemical assay

The brain tissues were separately homogenized in 8 ml of 50 mM of Tris-HCl buffer (pH 7.4) containing 1.15% potassium chloride. The homogenate was centrifuged at 10,000x g for 15 min at 4 ◦C. The supernatant was collected and subsequently used for total protein estimation. The protein content of the supernatant was estimated by the method of Lowry et al. (1951) using bovine serum albumin as a standard.

2.3.1 Assessment of Malondialdehyde

LPO was quantified as malondialdehyde (MDA), using the protocols of Farombi et al., (2000). The reaction contained tissue homogenates, 5% (w/v) butylated hydroxytoluene (BHT), 10% TCA and 0.75% TBA in 0.1 mol/L of HCl. MDA was calculated by using the following equation: $\sum = 1.56 = 105$ L/mol/cm, where $\sum$ is the extinction coefficient. Values are expressed in nmol/mg of protein or U/mg protein.

2.3.2 Assessment of Nitric oxide

Nitric oxide measured as nitrite was determined using Griess reagent, according to the method of Moshage et al. (1995). Briefly, 100 mL of sample were incubated with 100 mL of Griess reagent (Sigma) at room temperature for 20 min. Nitrite level was determined by measuring the absorbance at 550nm using a spectrophotometer.

2.3.3 Assessment of Reduced Glutathione

Reduced glutathione (GSH) content was determined using the Ellman (1959) method. Briefly, 1 mL of supernatant was treated with 500 µL of Ellman's reagent (19.8 mg of 5,5′dithiobisnitrobenzoic acid in 100 mL of 0.1% sodium citrate) and 3.0 mL of 0.2 M phosphate buffer (pH 8.0). The absorbance was read by a spectrophotometer at 412 nm.

2.4. Histology

Brain samples were fixed in 10% neutral buffered formalin and processed for routine tissue processing and H&E staining using established protocols (Bancroft & Gamble, 2008; Ijomone et al., 2018).

2.4.1 Image analysis of histological slides

Histological slides were digitized using a 20x objective with the Pannoramic 250 Flash II slide scanner (3D Histech, Budapest, Hungary). Non-overlapping images of the CA3 region of the hippocampus were captured using the CaseViewer software snapshot tool. Image Analysis and Processing for Java (Image J), a public domain software sponsored by the National Institute of Health (USA), was used to analyze and quantify photomicrographs. Image J cell counter tool was used to count the number of intact neurons. Intact neurons were identified by presence of distinct nucleoli and absence of neuronal degenerating features like pyknosis and vacuolations.

2.5 Statistical Analysis

Quantitative data were expressed as mean ± SEM. The significant difference between means for different groups were determined using Two-way Analysis of Variance (ANOVA) followed by Tukey's post hoc tests with GraphPad Prism Version 8 (GraphPad Inc, San Diego, USA) statistical software. A P value of < 0.05 was considered as statistically significant.

3.0 RESULTS

3.1 Malondialdehyde (MDA)

Two-way ANOVA data of the MDA activity (Figure 1) revealed no significant interaction ($F_{1,16}$=0.01874; P=0.08928), group factor ($F_{(1,16)}$=34.47; P<0.0001), and time factor ($F_{(1,16)}$=5.939; P=0.0269).

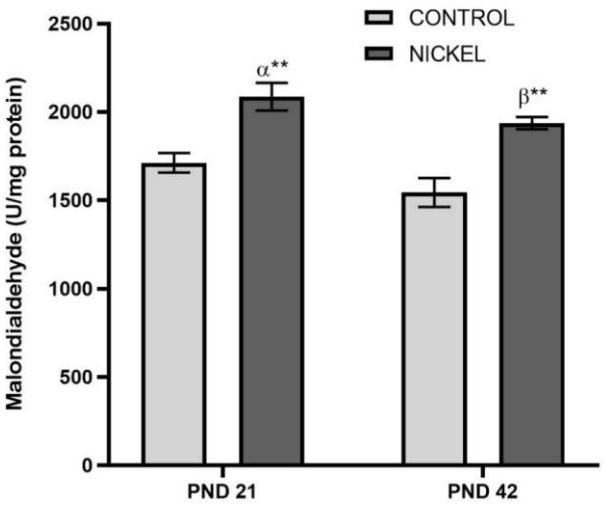

Figure 1. Prenatal exposure to Ni induced elevated MDA level in rat brain on postnatal days (PND) 21 and 42. Values are expressed as mean ± SEM **$P < 0.01$. α indicates significant difference from control on PND 21, β indicates significant difference from control on PND 42. Two-Way ANOVA followed by Tukey's post-tests

Post-test analysis revealed a significant increase (P< 0.0046) in MDA level on postnatal 21 in brain of pups prenatally exposed to Ni compared to the control. Similarly, there is significant increase (P=0.0031) in MDA level in the brains of pups from the Ni group compared to the control on postnatal day 42.

3.2 Nitric oxide (NO)

Two-way ANOVA data of the NO level (Figure 2) revealed no significant interaction ($F_{1,16}$=0.05664; P=0.08149), group factor ($F_{(1,16)}$=30.59; P<0.0001), and time factor ($F_{(1,16)}$=3.847; P=0.0675). Post-test analysis revealed a significant increase (P< 0.0044) in NO level on postnatal 21 in brain of pups prenatally exposed to Ni compared to the control. Similarly, there is significant increase (P=0.0086) in NO level in the brains of pups from the Ni group compared to the control on postnatal day 42.

3.2 Glutathione (GSH)

Two-way ANOVA data of the level of GSH (Figure 3) revealed significant interaction ($F_{(1,16)}$=5.088; P=0.0385), group factor ($F_{(1,16)}$=45.83; P<0.0001), and time factor ($F_{(1,16)}$=12.89; P=0.0017). Post-test analysis revealed a significant decrease (P< 0.0262) in GSH level on postnatal 21 in brain of pups prenatally exposed to Ni compared to the control. Similarly, there is significant decrease (P<0.0001) in GSH level in the brains of pups from the Ni group compared to the control on postnatal day 42.

3.3 Histology

The pyramidal neurons of the hippocampal CA3 in the Control group were well-arranged and closely packed. They possess normal cell morphology and size (Figure 4a). The hippocampal neurons that were prenatally exposed to nickel model group were arranged loosely, and exhibited cell body shrinkage, nuclear pyknosis, nuclear fragmentation, and nucleolar blurring and even disappearance. Following histomorphometry with Image J, Two-way ANOVA data of the number of intact neurons (Figure 4b) revealed

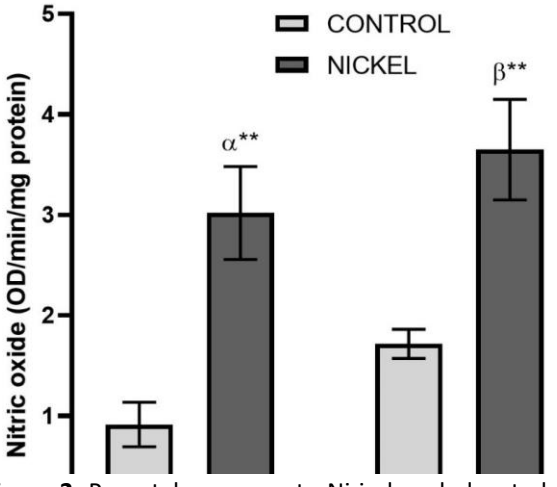

Figure 2. Prenatal exposure to Ni induced elevated NO level in rat brain on postnatal days (PND) 21 and 42. Values are expressed as mean ± SEM ***P* < 0.01. α indicates significant difference from control on PND 21, β indicates significant difference from control on PND 42. Two-Way ANOVA followed by Tukey's post-tests

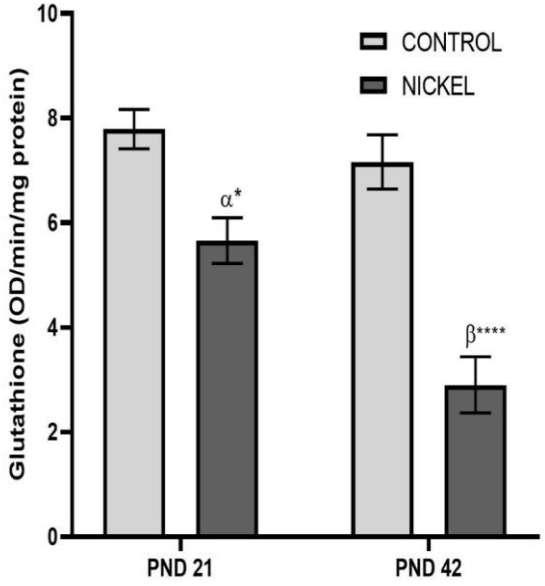

Figure 3. Prenatal exposure to Ni induced glutathione depletion in rat brain on postnatal days 21 and 42. Values are expressed as mean ± SEM **P* < 0.05, ***** *P*<0.0001. α indicates significant difference from control on PND 21, β indicates significant difference from control on PND 42. Two-Way ANOVA followed by Tukey's post-tests

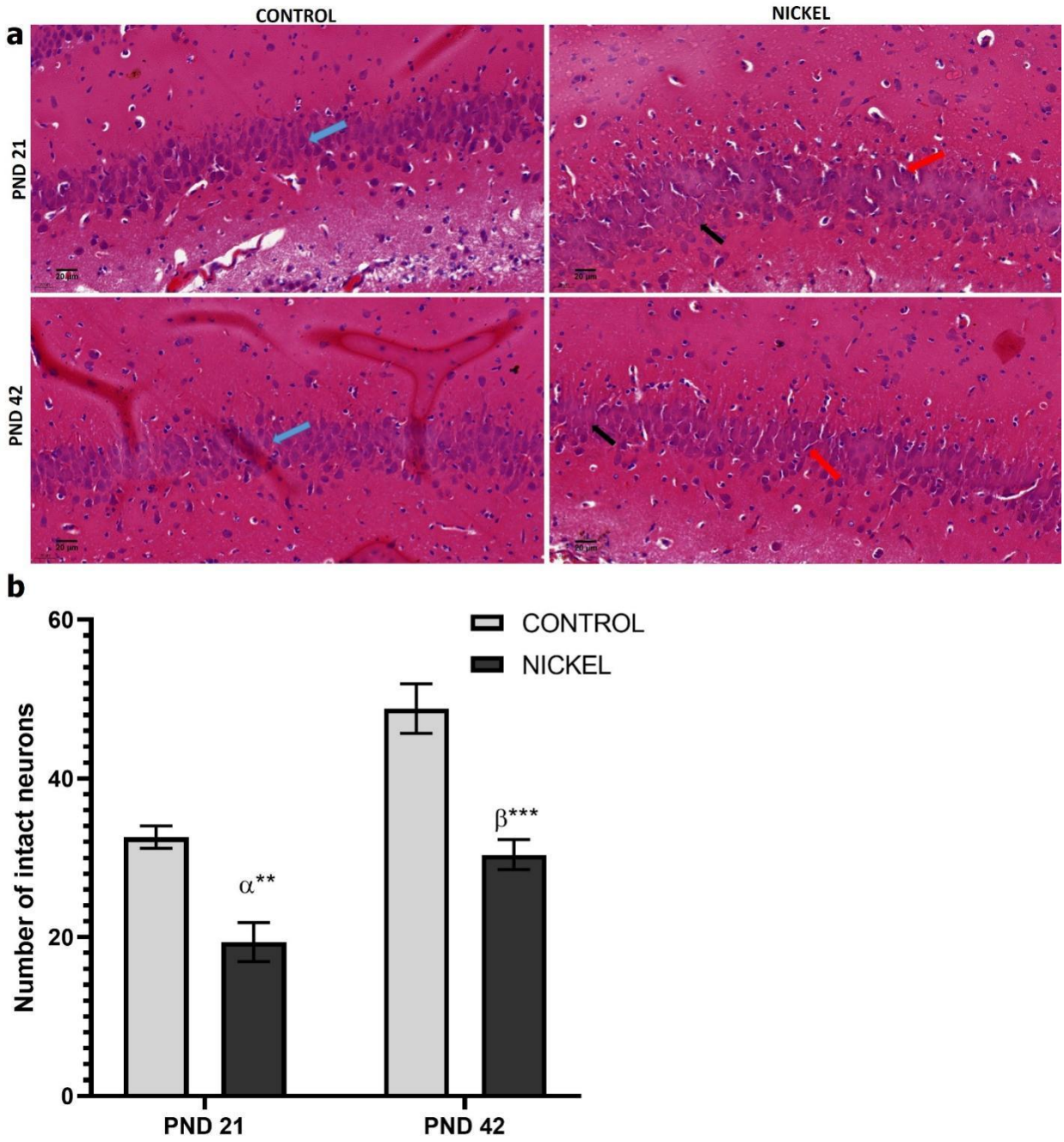

Figure 4 Prenatal exposure to Ni induced histological distortions in hippocampal CA3 on postnatal days 21 and 42. a - Representative photomicrograph of H&E; scale bars= 20 µm; red arrow- pyknosis, black arrow- absent nucleolus, blue arrow – intact neurons. b - Image J count of intact neurons. Values are expressed as mean ± SEM ***P*<0.01, ****P*<0.001. α indicates significant difference from control on PND 21, β indicates significant difference from control on PND 42. Two-Way ANOVA followed by Tukey's post-tests

significant interaction ($F_{(1,16)}$=1.268; P=0.2767), group factor ($F_{(1,16)}$=46.84; P<0.0001), and time factor ($F_{(1,16)}$=34.70; P<0.0001). Post-test analysis revealed a significant decrease (P< 0.0047) in number of intact neurons in the CA3 region of the hippocampus on postnatal 21 in brain of pups prenatally exposed to Ni compared to the control. Similarly, there is significant decrease (P<0.0002) in number of intact neurons in the hippocampal CA3 in the Ni group compared to the Control on postnatal day 42.

4.0 Discussion

This study investigated the effect of prenatal exposure to Ni on hippocampal development in postnatal life. A proven mechanism of metal neurotoxicity is oxidative stress, and Ni is not an exception (Ijomone et al., 2020b). The growing brain is particularly vulnerable to oxidative stress given that it has a high metabolic demand, consumes a significant amount of oxygen, and has a large amount of polyunsaturated fatty acids, which are targets for lipid peroxidation (Masjosthusmann et al., 2019). Oxidative stress arises when there is a dysregulation in the balance between the formation of reactive oxygen species (ROS) and the cellular antioxidant system's activity resulting in the buildup of ROS (Nishimura et al., 2021). Neurodevelopmental deficits are typically associated with ROS exposure during the fetal period (Wells et al., 2016). The findings from the study revealed an elevated level of MDA during postnatal brain development as recorded on PND 21 and PND 42. MDA is a free radical and product of lipid peroxidation (LPO), which results from the reaction of ROS with polyunsaturated fatty acid residues in membrane phospholipids (Banke et al., 2014; Siddique et al., 2012). LPO has been shown to be a contributing factor in Ni-induced cellular oxidative stress. Therefore, the rise in MDA concentration seen in this study implies that prenatal exposure of the brains to Ni could lead to an elevated brain lipoperoxidation and oxidative stress in during postnatal development. As is well known, LPO is a significant consequence of free radicals; excessive production of free radicals, including NO, superoxide anions, and hydroxyl radical (OH), can modify cellular lipids directly, potentially resulting in neuronal injury and a host of degenerative diseases of the central nervous system (Lamtai et al., 2020; Reena et al., 2012). Our findings also revealed elevated level of NO following prenatal exposure to Ni. Nitric oxide is a potent free radical known to be cytotoxic to neurons and glial cells (Lancaster, 1995; Osakada et al., 2003; Smith et al., 2005). Numerous studies have shown that NO can induced the progression of different neuro-developmental, neuropsychiatric and neurological disorders (Tripathi et al., 2020). In this study, prenatal exposure to 20 mg/kg Ni significantly increased brain nitrite levels. This suggests that maternal exposure to Ni during gestation could induced overproduction of free radical in the brain of the offspring in later life. During pathological circumstances and at high NO concentration, NO-derived radicals including peroxynitrite is produced in large amount and causes severe cellular impairments such as DNA oxidation and lipoperoxidation resulting in tissue injury and inflammation (Al-Megrin et al., 2020).

Apart from the direct quantification of free radicals, the reduction of the antioxidant glutathione (GSH) serves as an indirect indicator of oxidative stress. ROS, such as heavy metals, superoxides, peroxides, lipid peroxides, and free radicals, can seriously harm vital GSH-containing cellular components (Begum et al., 2022; Denkhaus & Salnikow, 2002). In nickel contaminated cells, a significant diminishing of GSH levels is reported (Begum et al., 2022; Denkhaus & Salnikow, 2002). Our results, which demonstrated a considerable decrease in GSH levels relative to the control, therefore suggests that Ni exposure to the mother during pregnancy may trigger oxidative stress in the growing brain, which may provoke neurodevelopmental impairment and eventually a neurodegenerative illness. Studies of the molecular and cellular events related to developmental neurotoxicity have identified a number of “adverse outcome pathways,” many of which share oxidative stress as a key event

(Nishimura et al., 2021). Moreso, the cytopathology of numerous neurodegenerative illnesses is primarily influenced by the production of free radicals and oxidative stress (Ebokaiwe & Farombi, 2015).

Furthermore, a growing number of experimental data demonstrated the critical role oxidative stress pathways play in neuronal death (Halliwell, 2006). The hippocampus is a brain region that is crucial for learning, memory, and emotion control (Jangra et al., 2014; Sulakhiya et al., 2014). Its high polyunsaturated lipid content, inadequate antioxidant defense, and massive oxygen consumption make it extremely susceptible to oxidative stress (Taniguti et al., 2018). The histological investigation in this study showed a high correlation with the redox imbalance. Microscopic analysis of the hippocampal CA3 showed that the control group had normal histological structures in infancy and adolescence. However, the pyramidal neurons in the CA3 region of the hippocampus of the Ni exposed rats showed significant features of histological damage to hippocampal neurons; likely brought on by the marked oxidative stress imposed by Ni treatment. In addition to damage at the molecular level that affects proteins, nucleic acids, and polyunsaturated fatty acids, oxidative stress can also cause changes in enzyme function, fluidity, ion transport, and protein synthesis, which can ultimately result in cellular degeneration (Curpan et al., 2021).

There is a large consensus that the prenatal environment determines the susceptibility to pathological conditions later in life. The hypothesis most widely accepted is that exposure to insults inducing adverse conditions in-utero may have negative effects on the development of target organs, disrupting homeostasis and increasing the risk of diseases at adulthood (Antonelli et al., 2017). The brain is particularly sensitive to alterations of the microenvironment during early development. Our study revealed that prenatal exposure to Ni significantly altered the brain redox homeostasis resulting histoarchitectural distortion and neuronal loss – a condition known to induce neurological disorders. Ni was shown to induce neuronal dysfunction via generation of reactive oxygen species (ROS) (Ebokaiwe et al., 2013). Reactive oxygen species target oxygen sensible lipids such as glycolipids, cholesterol, and phospholipids, which can undergo lipid peroxidation (Curpan et al., 2021). The ion gradient in cells can be affected when nonspecific lipid peroxides build up in membranes and disturb the bilayered structure of the membrane, hence altering its permeability and flexibility (Higdon et al., 2012). When these oxides are found in elevated quantities, 5-hydroxynonenal (4-HNE) and malondialdehyde (MDA) produce lesions to proteins, nucleic acids, and antioxidant molecules, eventually leading to the cell death (Higdon et al., 2012). In the present study, it appears the buildup of ROS in the brains of rats prenatally exposed to Ni overwhelmed the glutathione antioxidant defense, hence, the decline in recorded in GSH level. These biochemical alterations are corroborated by the oxidative damage and cell death noted in the hippocampal CA3.

In conclusion, the findings from the current study suggests that prenatal exposure to Nickel could provoke developmental neurotoxicity via oxidative stress by inducing lipid peroxidation and depleting the glutathione antioxidant system culminating in neuronal loss.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

AGT: Design, Methodology, Investigations, Data curation, Formal analysis, Project administration, Writing – original draft. IOK: Design, Methodology, Investigations. JSO: Methodology, Investigations. AAS: Methodology, Project administration, Resources. IOM: Conceptualization, Methodology, Formal analysis, Project administration, Resources, Writing – review and editing.

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