Reproductive Biology 20 (2020) 3–8

Contents lists available at ScienceDirect

Reproductive Biology

journal homepage: www.elsevier.com/locate/repbio

Review

Nickel toxicology with reference to male molecular reproductive physiology

Asim Rizvi, Saima Parveen, Saniyya Khan, Imrana Naseem*

Department of Biochemistry, Faculty of Life Sciences, Aligarh Muslim University, Aligarh, India

ARTICLE INFO

Keywords:
Nickel toxicity
ROS
Reproductive damage
DNA damage
Sperm viability

ABSTRACT

The toxicity of metals is a known phenomenon. Nickel toxicity is very common since nickel is used extensively both industrially and in items of personal use such as utensils and jewellery. Here we discuss human exposure to nickel and its toxicity in the light of the available scientific evidence to understand its underlying pathophysiology. The ability of Ni^{+2} to get oxidized to Ni^{+3} renders it's potential of generating reactive oxygen species (ROS) in the system leading to oxidative stress. Carcinogenesis, apoptosis induction, contact dermatitis, epigenetic changes, and alteration in gene regulation are a result of overexposure of nickel. Our focus is on how nickel affects the male reproductive physiology. Nickel primarily drives ROS mediated perturbations in the male reproductive system. It influences zinc metabolism, which is critical for sperm stability and affects the structure of DNA binding proteins, including protamines, thereby affecting sperm function.

1. Introduction

Nickel was first isolated by Axel Fredrik Cronstedt, a Swedish chemist in 1751 (Table. 1). It is sturdy white metal with magnetostrictive and ferromagnetic properties. It acquires 22nd place among earth's elements (0.008 % of earth's crust and 0.01 % of the igneous rocks) and 7th place among transition elements, 24 isotopes of nickel are known out of which five are naturally occurring [1]. Nickel occurs in various oxidation states, -1 being the lowest, +4 being the highest and +2 being the most common oxidative state [2]. Nickel naturally occurs as oxides and sulfides in volcanic dust, rocks, and soil. The unique physical and chemical properties render the extensive usage of nickel in the alloy industries and in metallurgical processes. Its unique biochemical properties make it indispensible for biological systems (Fig. 1).

The primary mode of nickel exposure in humans is via inhalation, dermal contact, and gastrointestinal ingestion. Particle size is a key determinant of its deposition in the body. Water-soluble nickel compounds are absorbed in the body through lungs by diffusion, whereas the water-insoluble nickel compounds enter the respiratory system by phagocytosis and remain in the lungs for a longer duration [2]. After entry into the body, the nickel gets accumulated in the kidney, which is the main target organ for deposition. Other organs where deposition of nickel takes place are lungs, brain, and pancreas. The transport of nickel in the body occurs by binding of the metal ion with specific proteins in the blood serum and its metabolism involves interconversion of nickel ions to various ionic forms. Nickel is known to interfere with the physiological processes of multiple metals which account for the physiological manifestation of its toxicity. Routes of excretion are urine and/or faeces depending upon the route of exposure and the ionic state of exposure [3].

2. Overview of general nickel toxicity

Occupational exposure of nickel is not uncommon, and usually causes immediate and delayed hypersensitivity. Nickel is a haemotoxic, immunotoxic, neurotoxic, genotoxic, nephrotoxic, hepatotoxic agent. It also causes reproductive toxicity and pulmonary toxicity besides being a carcinogenic agent [4]. Fig. 2 gives a brief summary of toxic biological manifestation of nickel accumulation inside human body. Acute nickel toxicity results in kidney injury, frank haematuria, nausea and vomiting. Chronic exposure results in hepatic and renal toxicities, hypothermia, bronchitis, rhinitis, renal tubular degeneration and incidences of reproductive and developmental toxicity [5]. International Agency for Research on Cancer [6] and U.S. Department of Health Human Services [7] has classified nickel compounds as a human carcinogen.

2.1. Carcinogenicity

The carcinogenic potential of nickel compounds depends on its solubility in water. Insoluble nickel compounds are known to be more potent carcinogens. The critical processes involved in the carcinogenic action of nickel compounds are oxidative stress, genomic DNA damage, epigenetic changes, and altered regulation of gene expression by

* Corresponding author.
E-mail address: imrananaseem2009@gmail.com (I. Naseem).

https://doi.org/10.1016/j.repbio.2019.11.005
Received 20 August 2019; Received in revised form 15 November 2019; Accepted 24 November 2019
Available online 28 December 2019

Table 1
Elemental properties of Nickel.

Atomic Number	28
Atomic Weight	58-71
Isotopes	5 stable; 19 unstable
Colour	Sliver White
Solubility	Dilute oxidizing acids
Occurrence	0.008 % of earth's crust as oxides and sulphides; 0.01 % of igneous rocks
Oxidation States	−1 to +4
Sources	Dust from volcanic eruptions; weathering of rocks and soil

activation of transcription factors [8]. Oxidative DNA damage as a result of nickel mediated ROS production, is critical for developing cancers and other terminal diseases. Other effects of nickel toxicity include induction of signal transduction and replication errors that all eventually lead to carcinogenesis [8–10]. A significant increase in the levels of 8-oxyguanine on nickel exposure as a result of DNA oxidation has been reported [11]. Various transcription factors such as NF-Kb, HIF-1, ATF-1, p53, and Rb protein are known to be stimulated in nickel transformed cells contributing to the deregulation of the cell cycle, cellular proliferation, elevated tumour growth, allergic effects which eventually leads to cancer.

2.2. Epigenetic changes

It was observed that both genetic and epigenetic abnormalities predate the start of cancer. Variation in genomic DNA independent of heritable patterns of gene expression are referred to as epigenetics [8]. DNA methylation induced by nickel results in epigenetic silencing or reactivation of gene expression, which leads to loss of H3 and H4 acetylation [8]. A recent study has proved that phosphorylation of serine 10 residues of histone is mediated by nickel. Many studies confirm that the binding of Ni^{2+} to N-terminal histidine -18 residues of histone H4 limits its acetylation.

2.3. Renal disorders

Significant accumulation of nickel occurs in the kidney, this results in various toxic effects on the body. Various studies have reported a decline in urine volume, urine glucose and rise in the level of nickel in the urine which may be linked to β_2 microglobulin levels [5] An increase in hematocrit (PCV %), hemoglobin concentration, and erythrocyte count [12] was also observed.

2.4. Neurotoxicity

Studies have shown that nickel toxicity results in neurological disorders such as giddiness and weakness. Experimental animals show signs of neurological toxicity on nickel exposure [13–15].

2.5. Effect on calcium homeostasis

Pulmonary toxicity of nickel is well established. In the lungs, interaction of nickel with cell surface receptors, specifically Ca^{2+} - sensing receptors (CaSR) activates cell signalling. This in turn, induce calcium and hypoxia-inducible pathway [12], which makes the cell survive in an anaerobic environment and ultimately enhances metastasis [16].

2.6. Respiratory disorders

Inhalation exposure of nickel results in respiratory distress as a consequence of bronchial and alveolar inflammation and congestion [17]. Epidemiological studies have reported increasing cases of nasal and lung cancer in nickel factory workers [8]. Studies indicate a close relationship between chronic bronchitis, lung cancers, and various other cancers with nickel exposure [18].

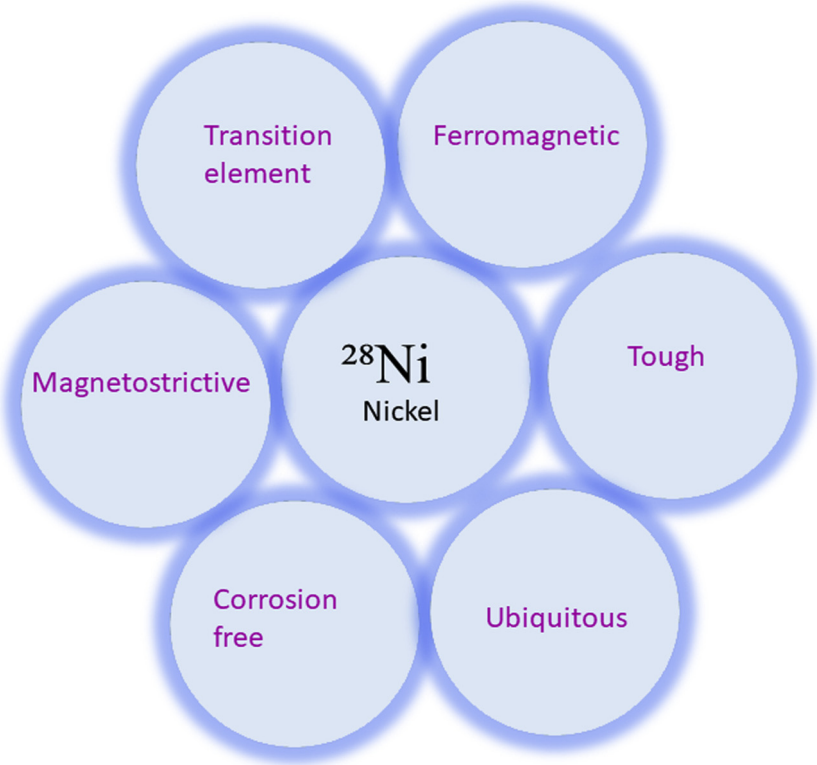

Fig. 1. Metallurgical and biological properties of Nickel.

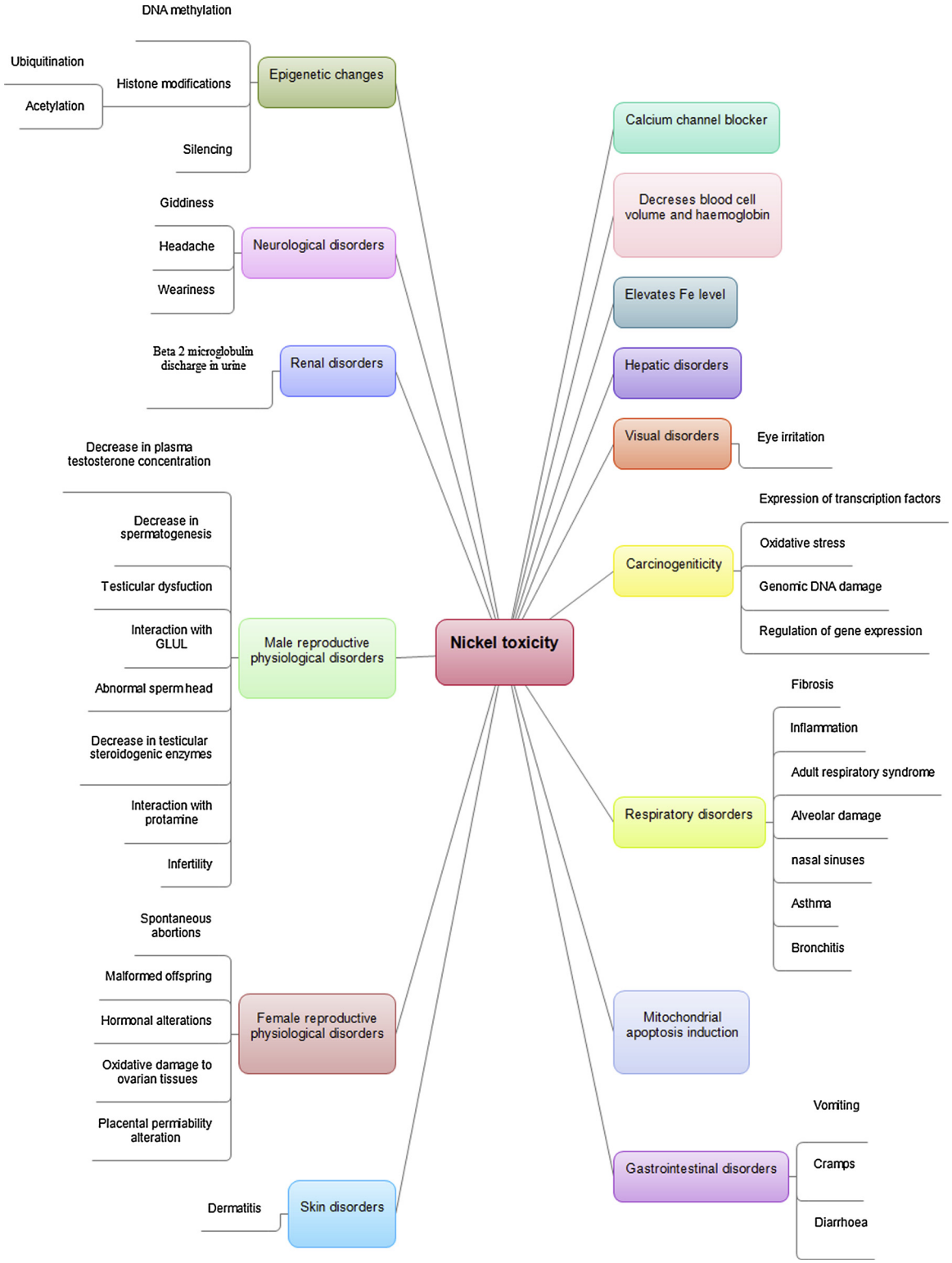

Fig. 2. Effects of Nickel exposure on the human body.

2.7. Embryotoxicity

Nickel is known to have embryotoxic effect as it can cross the placenta and may result in teratogenesis [19]. Nickel exposure is linked to decreased placenta viability, altered permeability, and potential embryotoxicity [8]. Developmental toxicity occurs also on nickel exposure. Decreased foetal body weight, malformed infant, increased spontaneous abortions have been reported in nickel treated animals [20].

2.8. Effects on female reproductive physiology

The adverse effects of nickel on female reproductive physiology are well documented and are beyond the scope of this review. Readers are referred to the following references [5,8,21–24], to develop a better understanding of this area.

Table 2
A review of previous work on Nickel toxicity to the male reproductive system: Human and animal studies.

S. No.	Title	Year	Key inferences with respect to male reproductive physiology
1	Nickel, its adverse health effects & oxidative stress [5]	2008	• Nickel sulphate and sulphide exposure leads to testicular degeneration • Testicular changes, such as interstitial cell proliferation, transport vessel walls, and reduced number of spermatozoa and some testicular enzymes such as steroid 3ß hydroxysteroid dehydrogenase. • Elevation in testicular lipid peroxidation; suppression in antioxidant enzyme
2.	Exploring the Molecular Mechanisms of Nickel-Induced Genotoxicity and Carcinogenicity: A Literature Review [8]	2011	• Nickel chloride exposure in male mice leads chromosomal aberrations and decrease in sperm count, increase in copper levels in testes; ROS mediated DNA damage, including base alteration, crosslinking, strand cleaving on nickel exposure.
3	Reproductive toxicology of nickel [21]	2012	• Dose-response decrease in absolute and organ to body weight ratios of testes, epididymes, seminal vesicles and prostrates upon nickel exposure • Decrease in sperm count and motility; alterations in various marker testicular enzymes such as sorbitol dehydrgenase, lactate dehydrogenase and gamma-glutamyl transpeptidase ; histopathological changes in testes, epidydimes and seminal vesicles. • Shrinkage of seminiferous tubules; decrease in number of basal spermatogonia. • On single dose of 20 or 40 mg/kg bw NiCl2 intraperitonally, destruction of regular testicular structure and dose-dependent variation in all morphometric indicators; decrease in height of germinal epithelium and diameter of seminiferous tubules and increase in diameters of lumen • A remarkable decrease in body weight, testicular weight, lactate dehydrogenase, protein concentration and increases in testicular glycogen and cholesterol on i.p. injection of 20 mg NiSO4/kg bw alternatively for 20 days in both normal and protein restricted diet. • A marked decrease in two testicular steroidogenic enzymes and concentration of plasma testosterone; increase in ascorbic acid and testicular cholesterol. • 48-h cultures of testicular interstitial cells obtained from the animals exposed to ≥ 20 mg/kg bw NiSO4 shows decrease in hCG stimulated testosterone response; no effects on histopathology of testes and epididymes. • Decrease in absolute and relative weights of testes, epididymes, prostrate glands and seminal vesicles on treating with 5, 10, or 20 mg/kg bw NiSO4 or NiCl2 orally (5 days/week) for 35 days; decrease in sperm motility at 10 and 20 mg/kg bw with both NiSO4 and NiCl2; decrease in sperm count at 20 mg/kg bw NiSO4; increase in sperm abnormalities at higher doses of both salts. • Decrease in cauda epididymal sperm count and sperm motility and testicular DNA, RNA and protein content on i.p. injection of 20 mg NiSO4/kg bw for 20 days (alternate days) • Dose-dependent increase lipid peroxidation in testis and epididymal sperm; increase antioxidant enzymes; dose-dependent decrease in double stranded DNA in the testis and in epididymal spermatozoa; dose-dependent increase in the percentage of abnormal sperms on i.p. 12.5, 25, or 50 µmol NiCl2/kg bw per day for 3 days; a remarkable increase in male-mediated dominant lethal-type mutations on mating nickel treated rats with untreated females for a duration of 5 weeks. • Spermatozoa losses it's spontaneous motility on treatment of motile(bull)sperm models with 0.66 mM NiSO4. • On nickel exposure a high positive co-relation between nickel content and separated tail of spermatozoa is present. • Medium to high positive corelation between nickel content and pathological spermatozoa. • On treating with NiCl2 (125–1000 µM) time and dose dependent decrease of spermatozoa motility; at the highest concentration and the longest time (240 min) of exposure apoptosis oocurs in the spermatozoa head. • Nickel chloride(1–5000 µM) treatment for 3 h leads to dose-dependent decrease in both hCG- and db-cAMP-stimulated testosterone production; increase in HCHOL- and PREG-stimulated testosterone production.125 µM or higher doses of nickel shows concentration-dependent decrease in hGC stimulated testosterone production. • Protective effect of histidine and cysteine is partial on high nickel exposure. • On treating H295R cell line for 48 h at 3.9 µM or higher dose of Ni^{2+} results in decrease in progesterone and testosterone production

3. Effect of nickel on the male reproductive system

The adverse effect of nickel on male reproductive physiology is established, and has been a subject of three reviews in the last ten years which are summarised in Table 2. On experimental nickel treatment a dose-dependent depression in both hCG and cAMP-stimulated testosterone production has been observed in rat interstitial (Leydig) cell culture [25,26]. The molecular mechanism of genotoxic activity of nickel compounds and the underlying mechanisms affecting male fertility is not fully understood yet. One plausible mechanism is the generation of reactive oxygen species (ROS), which initiates lipid peroxidation (LPO), whose products can create adducts with DNA, thus affecting gene expression. The degradation of peroxides of unsaturated fatty acids leads to the production of malondialdehyde (MDA). Higher doses of nickel induce moderate oxidative stress in testis, which is associated with apoptotic cell death and DNA damage in testis and epididymal sperm cells. ROS also known to cause severe pathological lesions and have a direct effect on spermatogenesis, thereby playing a significant role in the development of male infertility [27]. Cyclic nucleotide-gated channels (CNG) which are indispensable for sperm physiology are affected by nickel exposure [28]. Reduction in the number of spermatozoa and testicular enzymes such as the steroid 3β hydroxysteroid dehydrogenase along with severe changes in testicular pathophysiology, such as interstitial cell proliferation as a consequence of nickel exposure have been recorded [29]. Nickel treated rats showed a decrease in sperm count, sperm motility, and alteration of steroidogenesis [30], in addition to high testicular lipid peroxidation and suppressed antioxidant enzyme activity [31]. Supplementation of histidine and cysteine prevents nickel induced reduction in testosterone production [32]. The sperm cell is released from the testis with tightly supercoiled DNA which is transcriptionally inert [33], but it undergoes a profound change as it matures in the epididymis, capacitates in the

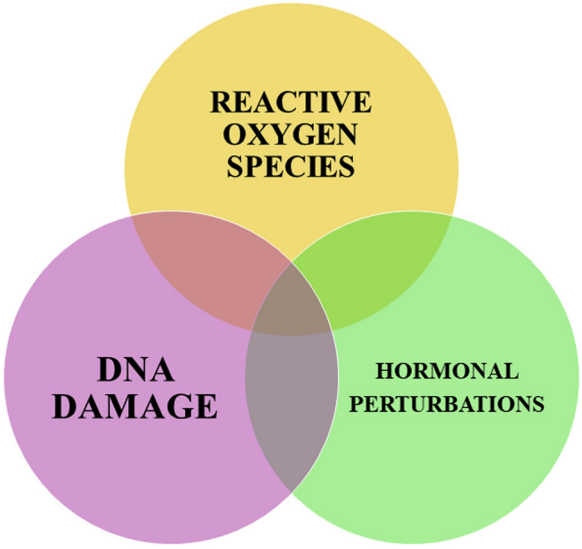

Fig. 3. Key players in nickel-induced reproductive toxicology.

female reproductive tract and fertilizes. Modifications in existing proteins achieve these changes.

Due to a limited amount of cytoplasm in mature sperm as well as high levels of unsaturated fatty acid (approx. 50 % of the fatty acid in human spermatozoa is docosahexaenoic acid with six double bonds per molecule), makes it more susceptible to oxidative stress [34]. An increase in abnormal sperms, a decrease in sperm count and fragmentation in sperm DNA is mediated by free radical-induced oxidative stress. These changes in sperm DNA leads to infertility. A significant positive correlation between the percentage of tail defects and blood nickel concentration was reported in welding workers on nickel exposure [35]. Studies show a possible decrease in the weight of testicular and accessory sex organs on nickel exposure [23]. Mature spermatozoa have the potential to exhibit many features of apoptosis, including activation of caspases 1, 3, 8 and 9, annexin-V binding and the mitochondrial generation of ROS [32].

Protamines, specifically protamine 2, is a target for nickel attack [36]. Protamine is a protein indispensable for the production and maturation of sperms in mammals. They are the most abundant sperm nuclear protein, and are positively charged. Protamines replace histone during spermiogenesis [37]. Protamines grant a higher order of DNA packaging in sperm than that found in somatic cells. The condensed and insoluble nature of the sperm chromatin protects the genetic message of the paternal genome. Protamines aid removal of transcription factors and proteins that help to reboot the imprinting code in oocyte during its transport through the male and female reproductive tracts [38].

Protamine replacement may also be necessary for the silencing of the paternal genome and reprogramming of the imprinting pattern of the gamete [39]. Protamines are phosphorylated as soon as they are synthesized and phosphorylation is prerequisite for the proper binding of DNA. In mammals, two types of protamines exist: the P1 protamine and the family of P2 protamines. The P1 protamine exists in all species of vertebrates whereas P2 family formed by the P2, P3, and P4 is known to exist only in some mammalian species including humans and mice [40,41]. Zinc is known to stabilize the chromatin through its binding to thiol groups not involved in forming disulfide bridges, which are in abundance in the sperm nucleus [41]. Hence, they might play a role in the normal functioning of the spermatozoon, and deficiency of zinc, or it's surplus, would result in variations [37]. Protamine 2 has a characteristic sequence of the Arg-Thr-His amino acids at their N terminus, which can be a trap for nickel and other heavy metals. Nickel binding to protamine 2 is firm and specific [42]. Nickel displaces zinc at the binding site of protamine. Nickel - protamine 2 complex prevents normal chromatin condensation. The lower level of the functional protein is probably the reason for male infertility, and the oxidative activity of nickel increases its interaction with P2 thus leads to changes in DNA structure and appearance of oxidation products, which are promutagens. Our laboratory is in the process of elucidating the biophysics of nickel-protamine 2 interaction (Parveen and Naseem, unpublished).

Studies carried out on males with undetectable P2 results in severe male infertility. In mice, haploinsufficiency of the protamines cause altered spermiogenesis, including lowered sperm counts and DNA damage [43]. Numerous studies have shown that an altered ratio of P1/P2, is associated with male infertility [44]. Diminished semen quality parameters, sperm functional ability, and sperm DNA integrity is due to dysregulation in human sperm protamine [43].

4. Developing a unified framework for the male reproductive toxicity of Nickel: conclusions and opinions

The reproductive toxicity of nickel is a much-studied field of research. However, the information seems scattered, and broader perspective vis-à-vis developing a unified framework for reproductive toxicity of nickel is needed. In this section, we have aimed to bring together facts to build our hypothesis on how nickel exerts its effects on reproduction (Fig. 3). It has been established beyond doubt that one of the primary mediators of nickel toxicity is reactive oxygen species (ROS) [8,25,45,46] and lipids/lipid products which have been oxidized by ROS, such as MDA. ROS are known to damage DNA by inducing base modifications, base loss, and damage to the phosphate-sugar backbone, such as the creation of single-strand and double-strand breaks. These perturbations in DNA structure can serve as the molecular basis of the carcinogenic action of nickel; however, this DNA damage by nickel assumes much higher relevance in context to the reproductive toxicity of nickel. The mature sperm cells have a very efficiently packed nucleus, which is present in the sperm head. Nickel mediated oxidation damages the sperm DNA, thereby making the sperm nonfunctional in case of apoptosis, or becomes a carrier of harmful mutations if it survives. The sperm, in any case, is a cell that is extremely susceptible to oxidative stress since it contains minimal cytoplasm (in the midpiece). The loss of cytoplasm during the evolution of the mammalian sperm increased its hydrodynamic ability, which is indispensable for fertilization, at the cost of cytoplasmic reduction, and hence making the sperm extremely susceptible to oxidative damage. Mild oxidative conditions are necessary for binding of the sperm to the zona pellucida and the acrosome reaction. Physiological concentrations of ROS enhance sperm capacitation by increasing cAMP synthesis and by inhibiting protein tyrosine phosphatases while activating tyrosine kinases. However, nickel mediated ROS production invariably leads to functional redundancy in sperms.

During the process of spermatogenesis, mammalian histones are progressively replaced by protamines for efficient DNA packaging. Nickel is known to interfere with protamine DNA interaction by altering the functional structure of protamines [36] specifically P2 and by competing with zinc [41] which is the physiological binding partner for protamine 2. This interference may result in inefficient DNA packaging in the sperm head, thereby making sperm DNA ‘loosely packed’ [41] and consequently more exposed to the reactive oxygen species and hence more susceptible to damage. There is also evidence of nickel affecting the physiology of the leydig cells [47].

This area seems to be mostly unexplored and could lead to insights into the molecular mechanisms of fetal nickel toxicity. In conclusion, the reproductive toxicity of nickel is primarily mediated by ROS induced DNA damage and perturbations in the hormone crosstalk. However, extensive research is still required to develop effective therapeutic strategies and interventions for nickel toxicity in the reproductive system.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgment

AR is a CSIR Research Associate and wishes to thank CSIR (India) for supporting this work. SK acknowledges UGC- New-Delhi for the award of MANF-SRF.

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