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Review article

Toxic effects of magnetic nanoparticles on normal cells and organs

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ABSTRACT

Magnetic nanoparticles (MNPs) are promising candidates for drug delivery and treatment of various disorders. Toxicity evaluation is a critical point in the development of nanoformulations and therefore, draws considerable attention. Formulations involving individual or combinatorial nanoparticle suspensions might be used for targeted delivery and treatment. This might be a evaluated further for safety related issues considering future medications based on MNPs. Nanoparticle distribution in the body is dependent on its surface characteristics. Size, dose and routes of nanoparticle entry have to be taken into consideration for future assays.

1. Introduction

Therapeutic nanoparticles have made an attempt to improve the efficacy as well as to reduce the toxicity of currently available drugs. They have been engineered to respond to the need of transporting drugs with higher target specificities [1]. The widespread use of nanoparticles for biomedical applications has led to an increased exposure of the MNPs through various routes to human and his environment [2]. The analysis of toxic effects of MNPs is therefore a pivotal area of research and need of the hour. Certain findings have thrown light on lethality of MNPs [3].

Though liver and spleen stand as major targets for MNPs administered intravenously, other organs and organ systems need to be evaluated for toxicity [4]. The current review, therefore, focuses on toxic effects of MNPs on normal cells and organs.

2. Therapeutic uses of different MNPs

Iron oxide nanoparticles (IONPs), the most commonly used MNPs for therapeutic applications, have specific properties such as superparamagnetism, high surface-to-volume ratio, greater surface area, and easy separation. They are known to play key roles in biomedical (primarily as MRI contrast agents), food and several other environment oriented applications [5]. The strong dipolar character of the surfaces of magnetite (γ-Fe_2O_3) nanoparticles and their thermal behaviors make them attractive biomedical agents [6]. They show multiple kinds of magnetic behaviors and hence, are applied in MRI, drug delivery systems and other therapeutic needs [7]. Such nanoparticles have also been used in waste water management and as immunological test systems [8,9]. Maghemite (Fe_3O_4) nanoparticles were considered as ferrofluids. However, recently, they are considered to be dispersed in a polymer matrix [10]. Since they are much more cytotoxic compared to γ-Fe_2O_3 nanoparticles, they are used in theranostic applications [11].

Zinc oxide nanoparticles (ZnO-NPs) are used in cosmetics, memory devices and catalysis. Although classified as ecotoxic by EU hazard classification, the US Food and Drug Administration has classified it to be safe for human use [12]. Cobalt oxide nanoparticles (Co_3O_4) are known to possess optical, magnetic and catalytic properties [13]. They are used for several applications such as in sensors, imaging and batteries [14,15]. Titanium dioxide nanoparticles (TiO_2 NPs) have been known to pose threats to humans, livestock, and the ecosystem since being used in drug delivery systems, antibacterial materials, cosmetics, sunscreens, and electronics. The International Agency for Research on Cancer (IARC) has classified TiO_2 NPs to be a Group 2B carcinogen for humans based on its exposure [16]. Silver nanoparticles (AgNPs) possess several physical, chemical and biological properties. They are used

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in industrial, household, and healthcare-related products [17]. Nickel nanoparticles (Ni NPs) have been widely known for storage and catalytic properties and possess super paramagnetic properties [18].

Cobalt ferrite nanoparticles (CoFe2O4 NPs) have been known to possess super paramagnetic properties and are currently used in data storage, imaging, drug delivery and catalysis [19]. Gold nanoparticles (AuNPs) are involved in drug delivery, imaging and therapeutic purposes, including diagnostics with several intrinsic properties [20,21].

3. Toxicity studies of MNPs

In six week old male ICR mice, MNPs within the size of 50 nm have been reported to be non-toxic even after staying in the body for a longer duration (4 weeks) at three different doses (100, 50, and 25 mg/kg) [22]. Though a moderate cytotoxic effect was observed in Vero cells after long (24 h) and short duration (4 h) exposures of various doses (10,000, 5000, 2500, 1250, 625, 313, 156 and 78 mg/ml) of IONPs. The outcomes did not show any larger abnormalities other than a slow weight gain. Very weak pulmonary fibrosis was observed in eight week old adult male wistar rats after intra tracheal instillation at a dose of 1 ml kg^{-1} body weight [23]. In L929 cell line (fibroblast connective tissue) MNPs were toxic to a certain extent. No abnormal clinical signs, tissue damage or weight loss was observed after testing for *in vivo* toxicity. Among the six week old male ICR mice used for a study, the MNPs were present in vital organs such as liver, heart, kidney and spleen at a dose of 10 mg/ml, after seven weeks of intravenous injection [24]. Fe_3O_4 paramagnetic nanoparticles exerted standard biocompatibility and limited toxicity in L929 cell line and a maximum inhibition rate of 78% against MCF-7 cell line. In Kunming mice model, diarrhea, reduced movements, loss of weight, and death in instant succession was observed after approximately 15 days. The doses were 1.77, 2.51, 3.54, 5.00, 7.06, 9.98, and 14.09 g/kg. LD_{50} value was 5.748 g/kg [25]. γ-Fe_2O_3 nanoparticles coated with polymers containing polyethylene oxide (5 and 15 kDa) were not toxic towards prostate cancer cell lines, human umbilical vein endothelial cells (HUVECs), and human retinal pigment epithelial cells (HRPEs) even after the nanoparticular uptake into such cells [26]. Polyampholyte-coated γ-Fe_2O_3 nanoparticles *in vivo* possessed biocompatibility, prolonged blood circulation and showed no toxicity on organs in mice after 14 days. The NPs were diluted to 0.138 mM and 138 mM with 0.9% NaCl and 0.2 ml was injected intravenously. *In vitro*, on HUVECs, these nanoparticles had no effect with regard to cell viability [27]. Fe_3O_4 nanoparticles had a protective effect on cadmium chloride induced liver toxicity by causing a reduction in Cadmium accumulation-induced oxidative damage in male Kunming mice at a dose of 30 mg/kg [28]. Thus, these reports speak for the MNPs to be better diagnostic and treatment aides.

There is an interesting report which suggests that when male wistar rats were administered orally with *Lactobacillus fermentum* containing Fe_3O_4 nanoparticles, it resulted in an elevated accumulation of such nanoparticles in the GI tract. This could help in better uptake of iron in the intestinal tract as a supplement [29]. In *Xenopus* and Zebrafish embryos, MNPs were specifically localized in the retinal pigmented epithelium layer when injected *via* the intravitreal route at 25 mg/mL concentration. Although the localization is specific it was not dependent on the characteristics of the particles [30]. These experiments have substantiated that although site-specific treatment is a major criterion for better application in medicine, it is not dependent on physical characteristics of the nanoparticles.

In an interesting study, AuNPs were accumulated in liver, whereas, AgNPs were accumulated more in major organs including heart, lung and kidney at a dose of 11.4–13.3 mg NPs/kg. Although accumulated, no toxic effects were observed over a two month period in 10–12 week old, adult male Kunming mice [31]. These studies showed that nanoparticles could be safer tools for targeted delivery to specific organs over longer periods of time.

4. Toxic effects of MNPs on normal cells and organs

MNPs have been known to possess protective effects against normal cells in certain studies as discussed in Section 3. Yet, the purpose of this section is to elucidate the toxic effects of such MNPs against multiple cells and organs.

4.1. Circulatory system

Acute intravenous administration of IONPs to BALB/C mice resulted in a procoagulatory effect *in vivo* and *in vitro*. It did also cause cardiac oxidative stress and DNA damage at a dose limit of 0.4, 2 and 10 μg/kg [32]. Fe_3O_4 nanoparticles at a LD_{50} dose of 163.60 mg/kg had induced denaturation and necrosis in cardiac muscles of ICR mice. The route of excretion was through liver. The nanoparticles would tend to stay for longer durations in major organs such as liver, heart, spleen, kidney and lungs for extended toxicity [33]. Healthy Sprague Dawley male rats were intravenously injected with Ni NPs of size 50 nm. 20 mg/kg of such nanoparticles implied cardiac toxicity in the form of arrhythmias. Damage to organs such as liver, spleen and lungs were also observed [34]. Female NMRI mice of 32–40 g weight range, administered with 300 mg/kg ZnO-NPs, showed considerable changes in the heart tissues without changes in the organ's weight [35]. CoFe2O4 NPs at varying concentrations exerted instable heart beat and cardiac/yolk sac edema in zebrafish embryos [3]. Flourescent MNPs exhibited extramedullary hematopoiesis in spleen of C57BL/6 male mice at a dose range of 159.4 to 319.5 mg/m^3 [36].

4.2. Digestive system

Zirconia oxide nanoparticles administered at a dose of 100 ppm to male wistar rats, resulted in liver damage [37]. Super paramagnetic iron oxide nanoparticles (SPIONs) were injected into CD1 female mice (8 weeks old) through the tail vein and manganese levels in liver, spleen, kidneys and brain were detected. Clearance of manganese levels were observed in spleen, kidney and brain after seven days, whereas, the manganese levels of liver stayed higher compared to the control group even after 3 weeks post injection of 150 μmol/kg [1]. Similar results supportive of liver toxicity were observed in other relevant experiments conducted on wild BALB/c mice and female albino wistar rats at 5 mg Fe/kg and 30, 300 and 1000 mg/kg body weight respectively [38,39]. The biodegradation and clearance of polyethylenimine IONPs in liver and spleen were comparatively lower to PEGylated nanoparticles. This was because PEGylated nanoparticles were much more tumor specific. Polyethylene glycol was a non-toxic encapsulating agent as demonstrated by the study. The dose was 100 and 500 μg/mL concentration for varying time durations [40].

4.3. Endocrine system

IONPs (150 μg/kg) administered orally to adult wistar male rats resulted in an increase in T3 thyroid hormone and caused a decrease in thyroid stimulating hormone [41]. This study indicated that MNPs could create an imbalance in the endocrine system.

4.4. Immune system

There was a considerable increase in the WBC count among 48 (24 male and 24 female) ICR mice that were administered with TiO_2 NPs (645 mg/kg) through the tail vein [42]. Magnetotactic bacteria synthesize magnetosomes, which are nanosized iron oxide particles surrounded by lipid membranes. Genotoxicity evaluation of magnetosomes (150 μg/ml) on WBCs showed that there were some chromosomal aberrations post-treatment [43]. Two week intravaginal instillation of γ-Fe_2O_3 nanoparticles could influence the immunological profiles of 14 week old adult female white mice (*Mus musculus*). Liver and spleen were the major organs influenced by the nanoparticles at a dose of 1.7 g Fe/kg [4].

4.5. Integumentary system

Gold coated magnetic (Fe_3O_4@Au) nanoparticles were moderately toxic in comparison to Fe_3O_4 nanoparticles at a concentration range higher than 500 μg/mL against primary human dermal fibroblasts (SKIN) and human epidermal keratinocytes (HaCaT cells) [44]. Colloidal suspensions based on IONPs produced significant alterations in *in vivo* dermal fibroblast profile, whereas, no alterations were observed in *in vitro* dermal fibroblast profile at a dose of 5, 10, and 25 μg·mL^{-1} [45]. Co_3O_4 NPs were cytotoxic to human derived HaCaT keratinocytes only after a long term exposure at varying doses of 1.5×10^{-7}–1.0×10^{-3} M with EC50 dose at 1.3×10^{-4} M for seven days [46].

4.6. Nervous system

With respect to toxicities associated with eye, the ocular toxicity of the MNPs, intraocular pressure, corneal endothelial cell count and retinal morphology were analyzed. After the administration of the MNPs intravitreally at 1.69 mg in Sprague-Dawley rats, little or no signs of toxicity were observed [47]. In an *in vivo* experiment conducted with guinea pigs, administration of super paramagnetic nanoparticles (SPNPs) (200 nm) did not affect the hearing threshold at day 7. Regarding ear toxicity, SPNPs of size 100 nm were toxic in comparison to 500 nm nanoparticles towards the inner ear derived from the ampulla of semicircular canals (EC5v cells). The final concentrations were 3×10^{10}, 3×10^9, and 3×10^8 MNP/ml for MNP-100 and of 7×10^8, 7×10^7, and 7×10^6 MNP/ml for MNP-500 [48]. Silica-coated SPNPs with an average diameter of 16 nm and a zeta potential of −15 to −20 mV were internalized at 1 mg/ml into epithelia of the tympanic membrane of albino guinea pigs (*Cavia porcellus*). Changes associated with the (intact) ossicular chain and tympanic membrane were equivalent to that of displacements created by 90 dB SPL in the human middle ear [49]. At higher doses such as 500 μg/mL, SPIONs may have an influence on cellular viability of hippocampal neural cells [50].

4.7. Reproductive system

Significant reductions in testicular cytology was observed through reductions in luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone levels in 40 Wistar adult male rats after a 14 day trial with manganese oxide nanoparticles at an oral dose of 100, 200, and 400 ppm [51]. Male and female Sprague-Dawley rats of 80–100 g exhibited inclination in LH, FSH levels and decline in estradiol levels (female rats) after treatment with Ni NPs for a period of ten weeks at a dose of 15 and 45 mg/kg. After exposure, the male rats were killed after experimental mating, whereas, the female rats were killed on the twenty second day of parturition. In the male rats, changes in weight, motility of rat sperm and the hormonal levels occurred, which confirmed the toxic effects of MNPs through the reproductive and developmental changes in offspring of rats [52]. Testicular tissue of mature NMRI mice exposed to ZnO-NPs showed reduction and loss of cells in seminiferous tubules at an intraperitoneal dose of 250, 500 and 700 mg/kg/day [53].

4.8. Respiratory system

Male C57Bl/6 mice (8 weeks old) were exposed to 2 mg/kg metal oxide nanoparticles by oropharyngeal aspiration. After 40 h of aspiration, severe inflammations occurred in mice lungs. In the same study, BEAS-2B lung normal cells exposed to various MNPs, (Co_3O_4, nickel oxide and TiO_2 NPs) showed pulmonary toxicity as assessed through several parameters. Surface coating with ethylenediamine tetra (methylene phosphonic acid) decreased its toxicity [54]. Pulmonary administration of IONPs resulted in changes in breathing, blood flow and inflammation among the lungs of adult male wistar rats, weighing about 250–300 g. Two different nanoparticle doses (20 and 40 mg/kg) and two different exposures (7 and 14 times) were applied for the experiment [55].

4.9. Urinary system

Several degenerations were observed along with the changes in urea and uric acid levels in kidneys of Wistar- adult- male rats when injected intraperitoneally with 30,50,70 mg/kg of TiO_2 NPs [56]. Vero (African green monkey kidney cell line), PK 15 (Pig kidney cell line) and MDBK (Madin-Darby bovine kidney cell line) cells exposed to ZnO-NPs, iron oxide and copper nanoparticles showed significant dose dependent effects (10 μg/100 μl to 50 μg/100 μl) on cell viability based on cell types [57]. Although NRK-52E rat kidney proximal tubular epithelial cells treated with CoFe2O4 NPs showed no cytotoxic effect, DNA damage was evident at higher concentrations of 0–1000 μg/mL [58].

5. Multiorgan toxicity

Cerium oxide nanoparticles exposed intratracheally at a dose of 0.5 mg/kg to male and female BALB/C mice, induced oxidative stress, inflammatory responses and DNA damage in major organs such as lung, heart, liver, kidney, spleen, and brain [59]. Blood samples and organs collected from 8 week old male wistar albino rats exposed to intratracheal instillation of ZnO-NPs at different time points showed dose dependent (1 or 5 mg kg^{-1} body weight) pulmonary and extra-pulmonary toxicities. Histopathology showed degeneration and necrosis after 1 week of instillation in multiple organs including lung, liver and kidneys. Heart, pancreas, and brain did not show any changes [60]. In a one year fate study, AuNPs coated with iron oxide (56 μg of iron and 14 μg of gold), were accumulated in liver and spleen of pathogen-free female 8 week old C57/Bl6 mice and their elimination from these organs was slow. Surface coating played a vital role in their elimination [61].

6. Overall toxicity profiling among various organ systems and the mechanisms

Cardiac arrhythmia is the most common damage associated with heart. Weight of the organ did not usually change considerably even though toxicity issues were attained (Section 4.1). Liver is the primary organ affected with respect to digestive system (Section 4.2). Imbalances in hormones and genotoxicity among WBCs could also occur (Sections 4.3 and 4.4). Long duration exposures of nanoparticles could induce damages in dermal profile (Section 4.5). Damages to eye, ear and developmental changes associated with the reproductive system were also observed (Sections 4.6 and 4.7). Pulmonary damages and damages associated to urinary profile was also noted (Sections 4.8 and 4.9). Multiorgan toxicities were also observed in certain studies (Section 5).

MNPs are known to activate oxidative stress, inflammation of cells and induce indirect damage among DNA of the living systems [62–65]. The interactions of MNPs with the biological systems induce toxicity due to their physicochemical properties. Generally, the size of MNPs is the predominant reason for the difficulty in clearance and distribution. Studies suggest that MNPs larger than 100 nm are trapped in liver and spleen *via* macrophage phagocytosis [40,66]. Spherical shaped nanoparticles are much less toxic compared to rod-shaped nanoparticles [11,67]. The toxicity of MNPs is initiated through the increase in intracellular reactive oxygen (ROS) level in the host cells. The upregulation of transcription of inflammatory genes such as tumor necrosis factor – α and IL (interleukins)-1, IL-6 and IL-8, by activating nuclear factor-kappa B (NF-κB) signalling, may also lead to elevated toxicity.

Table 1
Toxicity of magnetic nanoparticles against normal cells and organs.

S.·no	Type of nanoparticles	Route of administration	Target system	Mechanism involved in damage	References
Circulatory system					
1.	Iron oxide	Intravenous	Heart	Oxidative stress and DNA damage	[32]
2.	Iron oxide	Intravenous	Liver, spleen, lung	Denaturation and necrosis in cardiac muscle	[33]
3.	Nickel	Intravenous	Heart, liver, spleen and lungs	Cardiac arrhythmias	[34]
4.	Zinc oxide	Oral	Heart	No considerable changes in weight of heart	[35]
5.	Cobalt ferrite	Chemical exposure	Zebrafish embryos	Instable heart beat and edema	[3]
6.	Flourescent magnetic	Inhalation	Nose	Extramedullary hematopoiesis	[36]
Digestive system					
7.	Zirconia oxide	Intraperitoneal	Liver, kidney	Induction of ROS and oxidative stress	[37]
8.	Iron oxide	Intravenous	Liver, spleen, kidneys and brain	Increase in liver manganese levels	[1]
9.	Iron oxide	Intravenous	Liver and spleen	Increase of AST and ALT levels	[38]
10.	Iron oxide	Oral	Liver, kidney, brain	Oxidative stress	[39]
11.	Iron oxide	Intravenous	Liver and spleen	Hemolysis, increase in ALT	[40]
Endocrine system					
12.	Iron oxide	Oral	Thyroid gland	Hormonal imbalance	[41]
Immune system					
13.	Titanium dioxide	Intravenous	Brain, lung, spleen, liver and kidneys	Damage to multiple organs	[42]
14.	Iron oxide	Oral	Gills and muscles of fish	Chromosomal aberrations	[43]
15.	Iron oxide	Cell culture	Human skin fibroblasts	ROS generation and apoptosis	[44]
16.	Iron oxide	Topical application	SKH-1 mice	Changes in Skin hydration	[45]
17.	Cobalt oxide	Human Skin	Keratinocytes	Necrosis	[46]
18.	Magnetite	Vagina	White mice	Changes in immunological pattern	[4]
Nervous system					
19.	Super paramagnetic	Intravitreal	Sprague-Dawley rats	Limited ocular toxicity	[47]
20.	Super paramagnetic	Inner ear cell culture	EC5v cells	Necrosis	[48]
21.	Super paramagnetic	Ear implantation	Albino guinea pigs	Hearing displacements	[49]
Reproductive system					
22.	Manganese oxide	Oral	Wistar adult male rats	Hormonal imbalance	[51]
23.	Nickel	Oral	Sprague-Dawley rats	Hormonal imbalance	[52]
24.	Zinc oxide	Intraperitoneal	NMRI mice	Testicular damage	[53]
25.	Metal oxide	Oropharyngeal aspiration	C57Bl/6 mice	Lung inflammation	[54]
26.	Iron oxide	Pulmonary administration	Wistar rats	Lung inflammation	[55]
Urinary system					
27.	Titanium dioxide	Intraperitoneal	Male rats	Changes in urea and uric acid levels in kidney	[56]
28.	Zinc oxide, iron oxide and copper	Cell culture	PK 15 cells	Changes in metabolism, decrease in cell viability	[57]
29.	Cobalt ferrite	Cell culture	NRK-52E cells	DNA damage	[58]

Oxidative stress, DNA damage and apoptosis could be the plausible mechanisms behind the toxic effects of multiple types of MNPs (Table 1) [68]. Though there are still no clear theories or reports on toxicity of MNPs, it is hypothesized that MNPs affect the molecular and cellular mechanisms of the living cells causing oxidative stress, cellular genotoxicity and finally, programmed cell death. Therefore, the studies considered for this review determine the toxicity associated with the MNPs and the possible mechanisms involved.

The reduction in the size of MNPs will reduce the chances of trapping in spleen and renal port during transportation. Further, synthesis of ultra-small SPNPs will possess efficient removal or clearance from the reticuloendothelial system and slower opsonisation [40]. Surface coating of nanoparticles can therefore be a major strategy for limitation in toxicity associated with such nanoparticles [69]. Utilization of biological and chemical coating agents over the MNPs will maintain the colloidal instability. So far, different coating agents, specifically, polymers, dextrans, polyethylene glycol and pluronic acids were coated over MNPs to reduce the toxicity, improve distribution and stability of the nanoparticles in the blood stream of the human body [40]. The surface charges of MNPs would be altered by the functional groups present on the coating material, influencing absorption of protein and change in the biological behaviour of MNPs [70,71].

Major organs tend to be affected more due to extended toxicity of MNPs based on dose and duration of stay inside such organs. Physiochemical and structural properties of nanoparticles, biodegradation and clearance were therefore lower for MNPs encapsulated with certain agents.

7. Conclusion

The current review focused on the toxicological profiles of MNPs and tried deriving some conclusions. Although there are reports supportive of the toxic effects of MNPs to vital organs, they are either preliminary reports or inconclusive in the authors' opinion, for the fact that they propose the upcoming or budding researchers to consider future research approaches. Some reports stand supportive for multi-organ toxicities as evaluated by multiple hematological and biochemical parameters. Encapsulation or coating of MNPs will provide a nanoformulation with limited toxicity compared to the free MNPs. Therefore, precise and elaborate research about the route of synthesis of nanoparticles and multiorgan toxicity assays are the need of the hour. Though there are many reports supportive of the application oriented view of the MNPs, toxicity is one aspect that must be provided extra care during future research.

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Conflicts of interest

All the authors of this manuscript declare that there are no conflicts of interest.

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