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Developmental toxicity of carbon nanoparticles during embryogenesis in chicken

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Abstract

Nanoparticles (NPs) are very small particles present in a wide range of materials. There is a dearth of knowledge regarding their potential secondary effects on the health of living organisms and the environment. Increasing research attention, however, has been directed toward determining the effects on humans exposed to NPs in the environment. Although the majority of studies focus on adult animals or populations, embryos of various species are considered more susceptible to environmental effects and pollutants. Hence, research studies dealing mainly with the impacts of NPs on embryogenesis have emerged recently, as this has become a major concern. Chicken embryos occupy a special place among animal models used in toxicity and developmental investigations and have also contributed significantly to the fields of genetics, virology, immunology, cell biology, and cancer. Their rapid development and easy accessibility for experimental observance and manipulation are just a few of the advantages that have made them the vertebrate model of choice for more than two millennia. The early stages of chicken embryogenesis, which are characterized by rapid embryonic growth, provide a sensitive model for studying the possible toxic effects on organ development, body weight, and oxidative stress. The objective of this review was to evaluate the toxicity of various types of carbon black nanomaterials administered at the beginning of embryogenesis in a chicken embryo model. In addition, the effects of diamond and graphene NPs and carbon nanotubes are reviewed.

Keywords Nanotoxicity · Carbon black nanoparticles · Embryogenesis · Chicken

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Introduction

The rapid growth of nanotechnology has transformed numerous sectors of the biomedical, industrial, and biological fields, with breakthrough applications in the areas of biotechnology, electronics, cosmetics, biosensors, materials science, aerospace engineering, and medicinal drug delivery. Engineered nanoparticles have garnered commercial attention in a variety of consumer products. Their novel physicochemical, electrical, and thermal properties enable their use in medical science, cosmetics, and clothing, thus increasing the likelihood of human, animal, and environmental exposure to these NPs (Maynard et al. 2004; Donaldson et al. 2010) (Fig. 1). Because of the smaller size of NPs (< 100 nm), they are present in enormous numbers in typical ambient air, with levels in the range of 50,000–10,000 particles per /ml, rising during pollution episodes to 3 million particles/ml (Donaldson and Stone 2003), and their levels differ from region to region, and further from period to period in the same region (Richard et al. 2001). Despite the growing commercial interest in NPs, there have been only modest research efforts toward investigating the adverse effects of these NPs on the environment, humans, and animals. The large number of physicochemical parameters of NPs, such as shape, size, structure, and essential elements, makes investigation of their toxic effects complex and challenging (Poljak-Blaži et al. 2010). The expansion of nanotechnology has given rise to questions regarding the potential toxicity of NPs, the increased exposure to humans and release into the environment during their manufacture, and their appropriate use and disposal (Li et al. 2008). Studies on the influence of environmental particulates on human health have shown a link with NPs and ultrafine particles (diameter < 100nm) (Donaldson et al. 2005). Over the past few decades, many nanotoxicology studies have been undertaken to demonstrate the critical role of NPs and ultrafine particles in the induction of oxidative stress and their biological effects, particularly in relation to cellular toxicity (Donaldson and Stone 2003; Donaldson et al. 2005). Carbon-based nanoparticles (CNPs) such as graphene, carbon nanotubes (CNTs), diamond nanoparticles (DNPs), and carbon black NPs (CBNPs) have enabled numerous technological advances across a wide range of applications, from mechanical engineering to biomedicine and biological research (Magrez et al. 2006; Bhunia et al. 2013; Ali et al. 2016). Notably, CBNPs are one of the generality commercially pertinent forms of CNPs which have been well-categorized as carbonaceous particles (Utsunomiya et al. 2004; Jackson et al. 2012) as a result of their widespread environmental and industrial use for different purposes (Pumera 2010; Scida et al. 2011; Tiwari et al. 2015; Ramnani et al. 2016).

Chicken embryos of are considered a good model for experimental research, in particular because of the lack of maternal influences on embryogenesis and the rapid development, enabling accurate assessment of toxicity (Rashidi and Sottile 2009; Ribatti 2012). Past studies have indicated that exposure to NPs in the microenvironment is associated with adverse pregnancy outcomes including lower birth weight, premature birth, and small size for gestational age, especially with exposure during sensitive stages of development (Shah et al. 2011). The small size of NPs enables them to translocate from the external environment via cell membranes into organisms (Stone et al. 2007), and the direct transport of particles is one suggested mechanism by which NP exposure is thought to exert harmful effects on vital tissues (liver, heart, brain) during different stages of embryonic development (Kreyling et al.

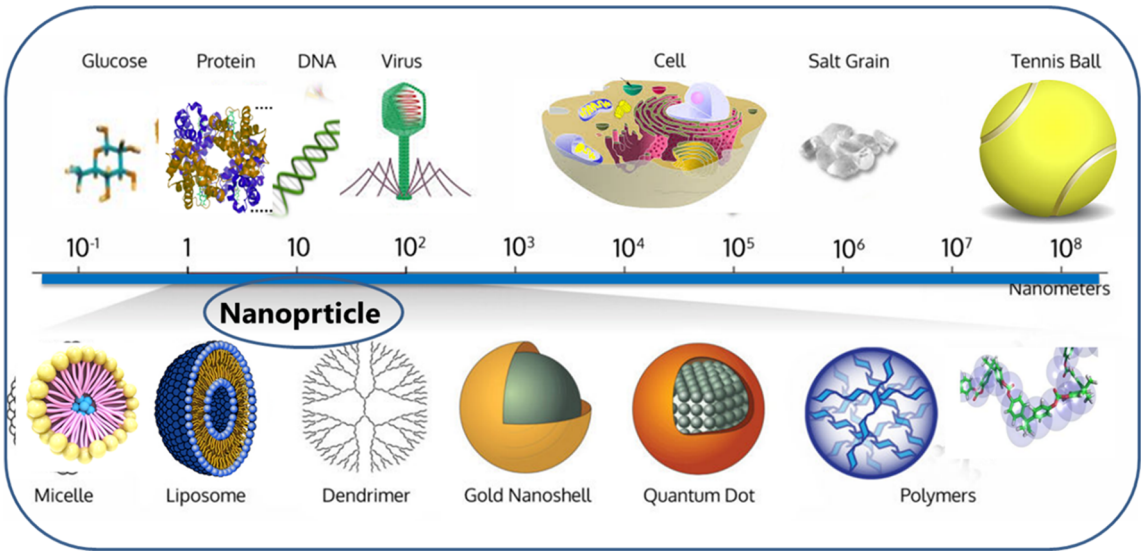

Fig. 1 The scale size of NPs. Length scale showing the size of NPs compared to biological materials (i.e., glucose, protein, DNA, virus, bacterium, and cells of nano and micro size. In the bottom panel, a few types of NPs are represented: micelle, liposome, dendrimer, gold nanoshell, quantum dot, and polymer NPs

2002; Sadauskas et al. 2007; Sadauskas et al. 2009). The aim of this paper was to highlight the toxicity of various CBNPs and carbon allotropes such as graphene, CNTs, and DNPs during embryogenesis in chickens when administered at different stages of embryonic development in the chicken embryo model on various organs.

Carbon black nanoparticle sources

CBNPs are widely used for industrial applications, with the tire industry consuming around 70% of CBNPs, and the remaining 30% for other rubber products and some non-rubber uses, such as black pigment in printing inks, through the processing of leather goods and electrodes for batteries in electrical conductors (IARC 2010). Additionally, combustion systems are a notable source of essential CBNPs, and CNPs with diameters less than 100nm constitute a major proportion of environmental pollution and diesel exhaust (Dörger and Krombach 2002; Möller et al. 2005).

With the rapidly increasing and widespread manufacture of CBNPs, it is necessary to focus our attention on understanding their potential toxicity and long-term effects on human health and well-being. Carbon black is a carbonaceous particle that has been widely used as a model for diesel emission particles without adhered metals and chemicals. Printex 90 NPs, for example, are CBNPs present in printing ink and have been used in several investigations of nanotoxicology. Printex 90 consists of carbon with less than 1% organic and inorganic impurities (Wilson et al. 2002). In vivo studies in mice and rats on the health effects of pulmonary exposure to CBNPs by inhalation or instillation have reported allergic or inflammatory effects (Jackson et al. 2012; El-Sayed et al. 2015). CBNPs possess an intrinsic ability to generate reactive oxygen species (ROS), which induces DNA strand breaks, oxidative DNA damage, and mutagenicity (Jacobsen et al. 2011), and have been shown to induce lung tumors in rats (Mohr et al. 2006). Inconclusive reports have indicated that exposure to carbon black may be associated with cancer risk; however, carbon black has been categorized by the International Agency for Research on Cancer (IARC) as likely carcinogenic to humans by (Baan et al. 2006).

Oxidative stress as an underlying mechanism for nanoparticle toxicity

The biological responses of cells such as the oxidative stress phenomenon occur because of the potential and abundance of ROS in organisms. It largely results from an imbalance between ROS release and the ability of the immune system to reduce the toxicity of free radicals or repair the resulting damage. A hierarchical model of oxidative stress was proposed to demonstrate the mechanism of action for NP-mediated oxidative stress (Li et al. 2008). Excess ROS, as a result of exposing tissues and cells to NPs, leads to increased oxidative stress and induces antioxidant enzymes. In the case of moderate oxidative stress conditions, transcriptional activation of antioxidant enzymes occurs through nuclear factor (erythroid-derived 2)-like 2 (Nrf2) induction.

At an intermediate level, redox-sensitive mitogen-activated protein kinase (MAPK) and nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) cascades induce a pro-inflammatory response. However, extremely toxic levels of oxidative stress result in electron transport chain dysfunction and mitochondrial membrane damage, followed by cell death. The key factors for the pro-oxidant influences of engineered NPs contain either the depletion of antioxidants or increased production of ROS that has harmful effects on cell constituents including lipids, proteins, or DNA (Huang et al. 2010). The oxidative stress due to NP exposure may increase the amount of lipid peroxidation, DNA damage, and stimulation of signaling networks associated with lack of cell growth, carcinogenesis, and fibrosis (Buzea et al. 2007). Moreover, ROS can result from reactions of NPs with many biological component targets as an effect of cell metabolism and respiration (Risom et al. 2005). NP-induced ROS reactions include activation of inflammatory cytokines, cell signaling pathways, specific transcription factors, and chemokine expression.

The cellular mechanisms induced by NPs are closely associated with transcription of genes contributing to genotoxicity, inflammation, cancer, and fibrosis (Manke et al. 2013). Thus, the pathological outcomes detected during NP exposure could be as a result of excessive ROS production. It is important to combine these various biological responses as a screening device for the toxic influences of NP. For example, overexpression of antioxidant enzymes indicates the onset oxidative stress effects of, where mitochondrial apoptosis occurs during disorders of toxic oxidative stress (Li et al. 2008). The NP exposure studies should include strict criteria for NPs and assign in vivo and in vitro oxidative stress indicators as toxicity endpoints as a predictive paradigm for risk evaluation (Li et al. 2010; Shvedova et al. 2012b).

Oxidative stress and antioxidants in the central nervous system

Pathological evidence of ROS-mediated neuronal damage shows the highest vulnerability to ROS in the biochemical composition of the nerve tissues, while including a group of unsaturated fatty acids susceptible to peroxidation and oxidative modification. Free radicals can attack the hot-spot regions of the unsaturated fatty acids, which are represented at double bonds, thus initiating cascades or chain reactions, leading to damage of neighboring unsaturated fatty acids (Butterfield

et al. 2002). It is well known that the brain consists of fatty acids in high concentrations which are more vulnerable to peroxidation, and despite its relatively low weight (2%), the brain consumes an inordinate fraction (20%) of oxygen uptake. Moreover, it is not principally enhanced in antioxidant enzyme defenses in comparison with other body organs or tissues, and so nerve cells are considered to be more susceptible to oxidative stress than other body tissues (Floyd and Carney 1992).

The antioxidant enzymes including glutathione peroxidase (GPx, EC 1.11.1.9), catalase (CAT, EC 1.11.1.6), and superoxide dismutase (SOD, EC 1.15.1.1) constitute the first line of defense against ROS, and reduction in their activity contributes to the harmful oxidative effects on the tissue (Fukai et al. 2002). The mechanisms of defense by antioxidant enzymes include scavenging of ROS species, removal of singlet oxygen or their precursors, inhibition of ROS generation, binding of metal ions required for the catalysis of ROS production, and up-regulation of endogenous enzymes. Antioxidant protective efficiency depends on the severity of the damage (Halliwell 1994, 1996), type of ROS formed, and the location of formation (body barriers such as the blood–brain barrier (BBB) reduce the permeability of most antioxidants).

Glutathione (GSH) is a tripeptide containing sulfur amino acid cysteine that has a reactive SH group with reductive capability. It can be connected with the enzymatic detoxification reflection for ROS generation, as a coenzyme or a cofactor, and it can also perform as a non-enzymatic antioxidant by the direct interface of the SH group with ROS (Gürer et al. 1998). In addition, it has the ability to scavenge free radicals, and is responsible for conserving the cellular redox event and protecting cells from oxidative damage (Rahman et al. 2005; Habib et al. 2007). NP-triggered ROS reduce GSH into its oxidized form glutathione disulfide (GSSG), thereby participating in apoptosis, oxidative stress, and sensitization to oxidization (Fenoglio et al. 2008). To one side GSH, NP-can be stimulate ROS changes the antioxidant efficacy of ROS-metabolizing enzymes including glutathione peroxidase, catalase, NADPH-dependent enzyme, and superoxide dismutase (SOD) (Stambe et al. 2004). SOD is one of the main antioxidant enzymes and is the most commonly investigated large protein molecule. SOD converts superoxide to hydrogen peroxide (H_2O_2).

Various forms of SOD have been reported. The first, at its active site, containing zinc and copper, can be found in the cytoplasm of cells. Also, an isoform of this molecule is found in extracellular fluids such as plasma. Another isoform is located in the cell mitochondria and contains manganese at its energetic spot (Zelko et al. 2002). Catalase is a peroxidase, is found in peroxisomes in most cells, and contains a heme group at its active site. Additionally, it is thought catalase is able to cross membranes easily and reduce hydrogen peroxide ($H_2O_2 \rightarrow H_2O + O_2$), which is directly formed by several enzymes, to water and oxygen. The activity of this enzyme is higher in the liver than the brain (García-Arellano et al. 2004).

Cellular signaling affected by nanoparticles

The primary pro-oxidant effects of NPs result in the activation of signaling pathways, transcription factors, and cytokine cascades involving a variety of cellular responses. The regulation of redox homeostasis requires signaling cascades such as HIF-1, MAPK NF-κB, and Pi3-kinase, which dominate metastasis, proliferation, cell growth, inflammation, and apoptosis (Li et al. 2010). With oxidative stress at a moderate level, pro-inflammatory pathways are stimulated in order to sustain the redox equilibrium. The pathogenesis of fibrosis is partly attributable to pro-fibrotic mediators such as TNF-α, IL-1β, and TGF-β. It is well documented that cells neutralize the overwhelming oxidative stress response via augmented cytokine expression such as TNF-α and interleukins, inhibition of phosphatases, and activation of kinases, thus manipulating the phosphorylation cascade (Fig. 2).

Protein phosphorylation is involved in the regulation of critical cellular responses including cell adhesion, mitogenesis, apoptosis, and oncogenic transformation. Thus ROS response seems to be highly related to factors leading to carcinogenesis (Genestra 2007). The NF-κB are a group of proteins that can stimulate genes responsible for defense against cellular oxidative stress and regulate miscellaneous functions such as immune response, inflammation, cell proliferation, and apoptosis. Pro-oxidant H_2O_2-mediated NF-κB activation over the traditional IKK-dependent pathway is well recognized. Oxidative stress such as OH, HOCl, and O_2 and reactive nitrogen species (RNS) such as ONOO− activate NF-κB via the release of IκBs, resulting in the nuclear translocation of NF-κB. Once inside the nucleus, NF-κB induces transcription of pro-inflammatory mediators (Allen and Tresini 2000).

CBNPs were found to enhance ROS in rat alveolar macrophages—an example where non-biodegradable components of CBNPs can generate an immune and oxidative stress response (Aam and Fonnum 2007). Another study showed excessive generation of ROS by monocytes upon exposure of CBNPs (Stone et al. 2000). It is already known that increased production of pro-inflammatory mediators is linked to the activation of specific transcription factors such as NF-kB through Ca^{2+} upregulation and ROS formation (Stone et al. 2000, Choi et al. 2001; Lu et al. 2012). One study suggested that ufCB triggers an increase in cytosolic Ca2+, possibly through entry of extracellular Ca^{2+} via the Ca^{2+} channels in the plasma membrane (Stone et al. 2000). Therefore, NPs activate the opening of Ca^{2+} channels by means of ROS (Szmidt et al. 2016). It has now been revealed that alterations

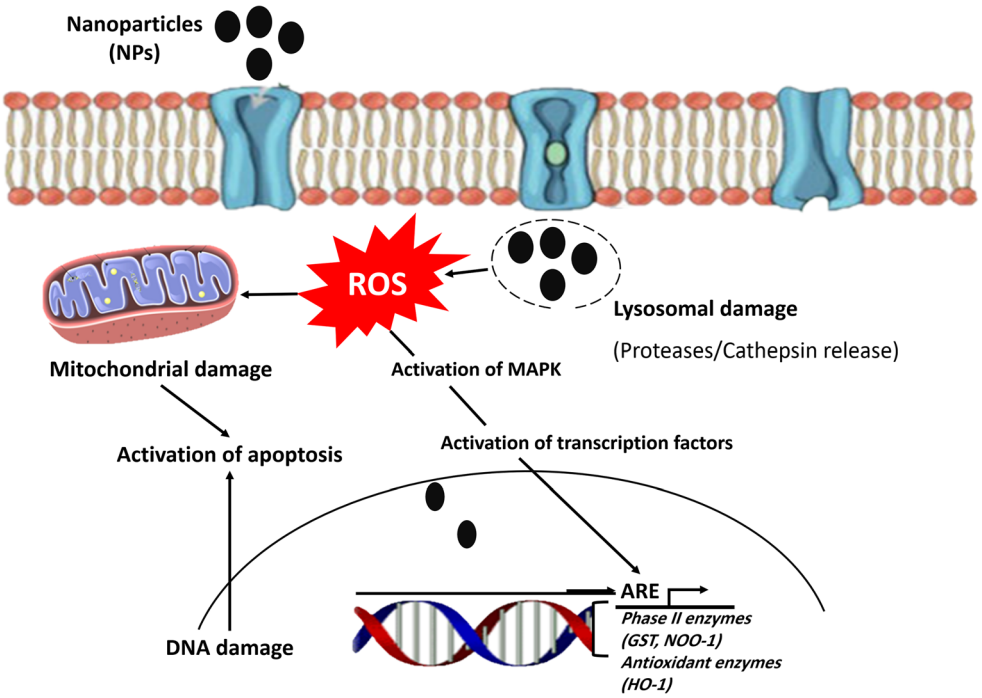

Fig. 2 Cellular mechanisms of nanoparticle toxicity

in glutathione and superoxide dismutase activity are the key enzymatic mechanisms involved in the generation of oxidative stress by CB (Zhen et al. 2017). CB-induced ROS involves many enzymatic reactions, including the ERK MAP kinase cascade pathway (Aam and Fonnum 2007). NADPH quinone oxidoreductase-1 enzyme was also found to be activated following diesel exhaust particle (DEP) exposure and mediated activation of ROS (Baulig et al. 2003). Oxidative stress produced by soot or CB is also linked with systemic immune response (inflammation) in the lungs, which results in the development of asthma and other diseases (Sarnat et al. 2011; Saber et al. 2012; Chan et al. 2013). DEP and CB also alter the expression of cell adhesion molecules and cause oxidative damage in human endothelial cells (Frikke-Schmidt et al. 2011).

Mechanisms of ROS production and apoptosis by nanoparticles

NP-induced oxidative stress causes apoptosis, which is primarily responsible for cell death (Hsin et al. 2008; Eom and Choi 2010). The major indicator influencing NPs which induce oxidative stress and cause cell death is apoptosis. There are various pathways by which apoptosis occurs; the intrinsic mitochondrial apoptotic pathway shows the main part in metal oxide NP-induced cell death. Thereby mitochondria are one of the main targets in cell organelles for NP-induced oxidative damage (Xia et al. 2006). The damage to membrane phospholipids stimulates depolarization of mitochondria, certainly owing to the high concentration of ROS in the mitochondria (Lenaz 2001) (Fig. 2).

A small rate of electrons escape through the mitochondria membrane and make contact with molecular oxygen to form $O^{2\cdot-}$, which later alters to H_2O_2 or slightly reduces to the deleterious $OH^{\cdot}$. NP can catalyze $O^{2\cdot}$ production either by delaying the electron transport chain or accelerating electron transfer to molecular oxygen (Boonstra and Post 2004). Exposure to CBNPs has been identified as a cause of cell death via increased oxidative stress in the cell.

Cell death can be caused in many ways, including pyroptosis, necrosis, and apoptosis. Increased production of ROS, decreased mitochondrial membrane potential, and DNA strand breaks have all been implicated in CBNP-induced apoptosis (Hussain et al. 2010). However, apoptosis is indispensable for many cellular processes, such as reducing inflammatory cells, but even incomplete or brief apoptosis may lead to extended infiltration of inflammatory cells in the lungs and may play a dominant role in several chronic disorders including lung inflammation (Hussain et al. 2010; Reisetter et al. 2011). One of the most frequently reported toxicity endpoints for CNTs is the formation of ROS, which can be either protective or harmful during biological interactions. Oxidative stress may be directly caused by CNT-induced ROS in the vicinity of or inside the cell, or may arise more indirectly due to the effects of internalized CNTs on mitochondrial respiration (Xia et al. 2007) or depletion of antioxidant species within the cell (Park et al. 2008). Moreover, NADPH-mediated ROS are critical for single-walled carbon nanotube (SWCNT)-induced pulmonary responses (Shvedova et al. 2008). The most likely mechanism for CNT-induced oxidative stress and lung toxicity

involves mitochondrial dysfunction. Incomplete phagocytosis of CNTs and the presence of transition metals and specific reactive groups on the surface of CNTs are key drivers of ROS generation. Metal impurities such as Fe, Co, and Ni introduced within the CNTs during their synthesis are major factors in CNT-mediated ROS response (Warheit et al. 2004; Le Goff et al. 2011). CNT-induced oxidative stress mediates important cellular processes including inflammation, cell injury, apoptosis, and activation of cellular signaling pathways such as MAPK and NF-κB which are implicated in the pathogenesis of lung fibrosis (Bonner 2002, 2007). For instance, SWCNT-dependent $OH^{\cdot}$ generation leads to activation of the molecular pathways MAPK, AP-1, NF-κB, and Akt associated with cell proliferation and tumor progression in vitro (Pacurari et al. 2008). Several studies have demonstrated that SWCNTs induce oxidative stress (Manna et al. 2005; Shvedova et al. 2012a; Azad et al. 2013). Similarly, exposure to multi-walled carbon nanotubes (MWCNTs) has been reported to induce ROS both in vitro and in vivo (Mitchell et al. 2007; Reddy et al. 2010; He et al. 2011; Clichici et al. 2012). Interestingly, oxidative stress is reported to be a mechanism for biodegradation of CNTs. SWCNTs undergo oxidative biodegradation via myeloperoxidase, a pro-oxidant enzyme involved in host defense responses (Shvedova et al. 2012a). Oxidative stress has been suggested to be an important factor in DNP toxicity (Stern and McNeil 2007). One study measured CAT and GSTPx activity, along with TAC levels, in order to evaluate the levels of oxidative stress. When oxidative stress was induced by the substances under study the level of ROS in the cells increased. CAT and GSTPx, which are antioxidants, help defend cells from the effects of interactions with ROS, such as free radicals (Yuan et al. 2010). DNPs that were administered to crickets at a relatively low dose with food did not cause significant differences in the levels of the parameters under study. The levels of HSP70 and TAC and CAT activity in the bodies of insects from the DNPs were comparable to values found in control animals. However, a significantly higher level of GSTPx activity in the gut and body fat may indicate that low doses of DNPs are not entirely safe or physiologically neutral (Karpeta-Kaczmarek et al. 2016). In animals exposed to lower concentrations of DNPs (20 mg g−1 food), there were few significant changes to these parameters. Analysis of DNA damage performed after 14 weeks using the comet assay revealed DNA instabilities in the insects, especially those that had been exposed to the higher doses of DNPs. These findings may suggest that the toxicity of DNPs is concentration-dependent. While high doses interact in a toxic manner, trace amounts, which are more likely in the environment, might be safe for organisms. Extreme caution should be taken, however, when handling DNPs (Karpeta-Kaczmarek et al. 2016).

The blood–brain barrier

The blood–brain barrier is a physical barrier that controls the entry of toxic matter and large molecules into the brain, thus maintaining a separation of the central nervous system (CNS) and systematic blood circulation. It is composed of tight junctions and adherence junctions, which selectively prevent the diffusion of pathogenic organisms, for instance, and hydrophilic molecules (Karagkiozaki et al. 2013). As observed in ultrastructural studies, there are key differences between the endothelial cells in the brain and those in most peripheral tissues, in two ways. First, they have very few endocytotic vesicles, thereby limiting the amount of transcellular flux. Second, they are connected by tight junctions that restrict paracellular flux and seal the intercellular cleft, as shown in Fig. 3. The BBB has long been considered the gatekeeper of the CNS, sustaining the fragile homeostasis of the brain. The endothelial cells of the BBB are composed of neurons, astrocytes, pericytes, and extracellular matrix, which together have been defined as the neurovascular unit. The individual constituents of the neurovascular unit function in concert to regulate ion gradients, microvascular permeability, toxin removal, nutrient consumption, and cerebral hemodynamics. Furthermore, a disruption in any of the individual constituents may contribute to BBB dysfunction (Sandoval and Witt 2008). The BBB is an eclectic barrier consisting of capillary endothelial cells combined with each other surrounded by a basal lamina and/or by tight junctions. Blood capillaries in the brain are surrounded by and related to different types of cells, including pericytes, which are sheathed in neuronal processes, and the basal lamina that can extend to the BBB, releasing vasoactive neurotransmitters, perivascular endfeet of astrocytes near the outer surface of the basal lamina, and peptides (Fig. 3).

The BBB is one of the main interfaces between neural tissue and blood in higher vertebrates, including birds and mammals. Tight junctions of the BBB restrict the paracellular motion of polar solutes and ions from the blood to the brain and vice versa by blocking the transport of molecules of higher weight to the CNS (Saunders et al. 2008; Engelhardt and Sorokin 2009; Abbott et al. 2010). Thus tight junctions contribute to the formation and maintenance of a specific intracerebral homeostasis, with a close network of neurons and non-neuron types (e.g., pericytes, neurons, astrocytes, and microglia) and the extracellular matrix (ECM), a complex generally referred to as the neurovascular unit (Hawkins and Davis 2005). Oxidative stress can cause disturbance of tight

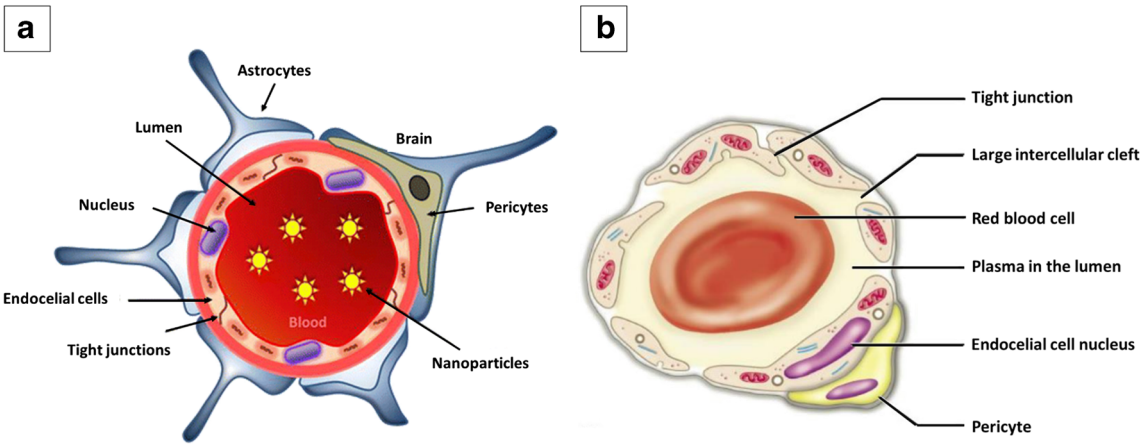

Fig. 3 Schematic representation of the structural differences between the **a** neurovascular unit of the blood–brain barrier and **b** normal blood capillaries. The nanoparticles, shown in the lumen of the blood vessel, must bypass the blood–brain barrier to enter the central nervous system (Mc Carthy et al. 2015). Normal blood capillaries lack pores, but adjacent endothelial cells exhibit some wider intercellular gaps which permit some fluid exchange between the plasma and tissue fluid by transfer between adjoining endothelial cells; they often have an irregular and broad cross section

junctions, leading to damage to the BBB and compromising the CNS (Lochhead et al. 2010).

Defense against oxidative disturbances in the cells requires coordinated interaction among the cells and framing the BBB. In this respect, astrocyte cells were found to be less vulnerable to oxidative stress compared to choroidal endothelial cells (CECs), and may defend and maintain the integrity of the BBB during oxidative damage (Bresgen et al. 2003). Additionally, astrocytes are linked to the regulation of neuronal glutathione homeostasis and, in this way, may participate in neuronal protection during oxidative stress (Watts et al. 2005). Pericytes are relevant to the cerebral blood capillary wall, and they have been investigated broadly (Krueger and Bechmann 2010). Pericytes appear to play a supportive function in the BBB, but they were revealed to exhibit continued shrinkage upon ischemia-induced oxidative stress, which negatively affects the survival of neuronal tissue and prevents restoration of the cerebral microcirculation (Yemisci et al. 2009).

As mentioned earlier, in the CNS, modification of endothelial cell activity may alter the permeability of the BBB, allowing the brain to be invaded by vasoactive material, toxins, neuro-inflammatory molecules, and other immunologically active constituents that consequently affect glial and/or neuron cells (Sharma and Sharma 2013). Likewise, the entrance of proteins stimulates the water channel in the brain parenchyma, causing cell injury, genesis of edema, and eventually cell death. It has been shown that metallic NPs can dramatically alter BBB function and permeability in animal cell models and induce notable cerebral edema in brain areas related to BBB damage. Furthermore, in these brain regions, glial cell activation, neuronal cell injury, loss of myelinated fibers, and heat shock protein upregulation are quite frequent, indicating that the changes of the BBB may also lead to neurodegenerative and neuro-inflammatory processes (Sharma et al. 2009). Very few studies have discussed how graphene materials pass through the BBB and cause neurotoxicity; thus further investigation is highly warranted.

Studies on the impact of nano-carbon on embryo development in chickens

In biological, biomedical, and toxicity investigations, chicken embryos are considered an ideal model, offering ease of use and accessibility (Rashidi and Sottile 2009). Also, they are characterized by short developmental life span and provide a high number of replicates, thus enabling accurate results to be obtained. The development of embryos is rapid and independent of the mother, and individual developmental stages are morphologically well evidenced, which makes the assessment among trials easier. Furthermore, because of the potential for large-scale tests with simple in vivo manipulations through various developmental stages, it is a suitable approach for toxicity testing. During embryonic development, the yolk sac provides nutrition for the embryo, transporting nutrients via the endodermal layer, as well as metabolization of maternal macromolecules such as the mesoderm layer, which produces the first blood cells within blood islands. We hold that the newly formed (small) islands are the basis for the enlargement and branching of the network of the yolk sac blood vessels which underpins normal embryogenesis. Table 1 summarizes studies on the effects of nano-carbon on embryogenesis in chickens.

CNPs such as graphite NPs (GNPs), DNPs, graphene oxide (GO), reduced GO (rGO), and pristine graphene (pG) are carbon allotropes that are suitable key materials for several industrial and medical applications, owing to their unrivaled combinations of physical and chemical properties. CNPs are used extensively in biomedicine and biological research,

Table 1 Summary of studies on the impact of nano-carbon on chicken embryogenesis

Form of nano-carbon (dose)	Treatments	Effects	References
Pristine graphene (50, 100, 500, 1000, and 10,000 μg/L)	Pristine graphene injected into fertilized chicken eggs, followed by incubation for 19 days	- Decreased survival rate - Body/organ weight and blood serum biochemical constituents not affected	Sawosz et al. (2014)
Single-walled carbon nano-tubes (30 μ/ml)	Treatment with mixed glial-neuronal cultures derived from chicken embryonic SPC or DRG	- Decreased the number of glial cells in both CNS and peripheral nervous system (PNS)-derived cultures - Decreased overall DNA content and reduced number of neurons	Belyanskaya et al. (2009)
DNPs	Administered in vivo to the tumor after 7 days of incubation	- Reduced volume, mass, and number of blood vessels in glioblastoma multiforme tumor cultured on chorioallantoic membrane (CAM)	Grodzik et al. (2011)
L-glutamine (Gln) and NDPs	Injection of Gln or ND and Gln/ND solution (50 mg/L) into fertilized broiler chicken eggs continuously from the first days to the end of embryogenesis	GLn, ND hastened maturation and growth of muscle cells	Grodzik et al. (2013)
DNPs (average dose of 0.3, 3.3, and 32.8 g/kg body weight)	DNPs injected into eggs	- No influence on either serum indicators or body/heart weight of the embryos' health. - Vascularization of the heart and the density of branched vessels significantly reduced after treatment with DNPs	Wierzbicki et al. (2013)
DNPs and carbon nanowires (CNW)	ND and CNW were injected into the yolk sac of embryos on the third day of incubation	- Visual impairment in embryogenesis that started from the early incubation period - ND showed gradual deterioration of the embryo's condition with the manifestations of the pathology in the temporary organs and body of embryos - Both types of nanostructures caused sublethal and irreversible morphologic changes	Lavrinenko et al. (2016b)
Functionalized multi-walled CNTs (fMWCNTs) and functionalized oxygen-doped multi-walled CNTs (fCOxs)		- Severe embryotoxicity in chicken embryos that were treated with fMWCNTs, while fCOxs seemed to exert cardio-embryotoxicity and discrete teratogenicity	Lara-Martínez et al. (2017)
Carbon black and chrysotile asbestos (14 mg/kg of weight)	Injection of the yolk in the first 3 days of incubation	- Caused underdevelopment of embryos and vessel depletion in blood islands of the yolk sac - Soot particles caused loss of vessel integrity and led to extravasation	Zinabadinova et al. (2018)
CBNPs (95,190, and 285 μg/ml CBNPs) equivalent (4.8, 9.5, and 14 μg/egg)	CBNPs were inoculated at the beginning of embryogenesis	- Induced oxidative stress - Augmentation of lipid peroxides and decreased glutathione and whole antioxidant capacity concentrations, as well as the activity of catalase - In the brain, mRNA transcript contents of antioxidant genes indicated up-regulation of superoxide dismutase-1 and heme oxygenase-1, with notably decreased regulation of glutathione S transferase-α expression - In pro-inflammatory genes, interferon-γ was down-regulated, while nuclear factor-κB1 was highly expressed. - Minor expression in apoptotic outcomes; for instance, caspase-3 and -8, B-cell CLL/lymphoma 2, and cytochrome c	Samak et al. (2018)

Table 1 (continued)

Form of nano-carbon (dose)	Treatments	Effects	References
		at several levels, while up-regulated expression of caspase-2 shown only at higher levels	
DNPs, placebo, graphite NPs, pristine graphene, large graphene oxide, small graphene oxide, and reduced graphene oxide (500 μg/mL)	Injected into albumin of fertilized chicken eggs	- Reduction of embryo survival. - CNP types can remain in blood circulation without any significant side effects - Proposed their effective use as vehicles for active compounds or drug delivery per second	Kurantowicz et al. (2017)
Graphene: GO, pG, and reduced rGO (50, 500, and 5000 μg/ml)	Injected into fertilized chicken eggs	- Embryo survival decreased considerably with all types of graphene - Body/organ weight slightly altered as influence of highest doses of graphene - Significantly decreased 8-hydroxy-2′deoxyguanosine (8-OHdG) after pG and rGO treatments	Szmidt et al. (2016)

including cell and tissue imaging, tissue engineering, and drug delivery, although reports concerning their toxicity are conflicting. Therefore, accurate categorization of their toxicity and biocompatibility is still needed to ensure safe and responsible use of these materials. Given their exceptional atomic structure, their electronic, mechanical, and optical properties, easy functionalization, and high surface-area-to-volume ratios (Du et al. 2014; Koromilas et al. 2014), CNTs have been widely used in multi-faceted applications. CNT toxicity in both in vitro and in vivo investigations has been attributed to several factors, including CNT length and aspect ratio, metal pollution level, period of exposure, mechanism of exposure, functionalization, and even the dispersant used to solubilize the nanotubes (Fenoglio et al. 2008; Firme and Bandaru 2010). The factors related to CNT toxicity remain uncertain, and discrepancies may be related to doses or species of animals and/or experimental protocols, although some perspectives have coincided. In a study conducted by Lim et al. (2011), the dosing formulation was not evaluated to conclude the degree of re-aggregation, nor were blood levels of CNTs assessed in the treated animals to confirm absorption.

Over the past decade, a number of in vivo and in vitro studies have examined CNT toxicity (Rivera Gil et al. 2010; Su et al. 2013; Chen et al. 2015). Xiao-feng et al. (2006) investigated CNT effects and their toxicity during the proliferating state of chicken embryo fibroblast cells. They found only slight toxicity of the CNTs to the chicken embryo fibroblast cells, around a first-degree impact (or score). Additionally, Belyanskaya et al. (2009) reported the effects of SWCNTs on primary cultures derived from of chicken embryonic dorsal root ganglia or spinal cord. SWCNTs significantly reduced the number of glial cells in both CNS- and peripheral nervous system (PNS)-derived cultures; the overall DNA content reduced the number of neurons. Moreover, whole-cell patch recordings showed a reduced inward conductivity and a more positive resting membrane potential of SWCNT-treated DRG-derived neurons compared to control groups. Overall, it has been observed that acutely toxic features in principal cultures from both the PNS and CNS of chicken embryos has been induced (Belyanskaya et al. 2009). SWCNT toxicity levels are dependent on the agglomeration state of the tubes; thus, if they are not able to enter the nerve cell through cell membranes at sufficiently high levels, it is likely that adverse effects on neurons and glial cells will occur.

SWCNT application was found to cause death of chicken embryos before day 12 of incubation, as SWCNTs inhibited the growth of blood vessels of the chorioallantoic membrane during embryonic development. Also, embryos were smaller, although without notable morphological abnormalities. Genes responsible for the regulation of apoptosis, cell proliferation, angiogenesis, and survival were found to be down-regulated (Roman et al. 2013).

Grodzik et al. 2011 studied the effects of DNPs on glioblastoma multiforme (GBM), the most common primary malignant brain tumor, with a uniformly poor prognosis. DNPs are bioactive elements toward glioma tumors cultured on the chorioallantoic membrane (CAM) of the chicken embryo. The authors found that DNPs reduced the volume, mass, and number of blood vessels in GBM tumors cultured on CAM, and also caused changes in the tumor ultrastructure. In a subsequent work, Grodzik et al. (2013) investigated the effect of L-glutamine (Gln) and DNPs on the expression of differentiation and growth factors of chicken embryo pectoral muscles. Fertilized broiler chicken eggs were injected with Gln or DNPs and Gln/DNP solution (50 mg L^{-1}) on the first day of embryogenesis continuously the end of embryogenesis, with results suggesting that the bio-complex of DNPs and Gln

could hasten maturation and growth of muscle cells. In studying the effects of graphite and DNPs on chicken embryo development, as well as vascularization of the heart and the chorioallantoic membrane at the molecular level, Wierzbicki et al. (2013) found no influence of either serum indicators or body/heart weight with regard to the embryos' health. Conversely, there is significant reduction in the heart vascularization and the density of branched blood vessels affected by contact with DNPs and, to a lesser extent, GNPs. Based on the above-mentioned reports, the use of NPs significantly reduced protein and gene expression of the pro-angiogenic basic fibroblast growth factor, demonstrating that both GNPs and DNPs prevent angiogenesis.

Sawosz et al. (2014) injected pristine graphene into fertilized chicken eggs, and the eggs were incubated for 19 days. Although survival rates were decreased at all doses, body/organ weight and blood serum biochemical constituents were not affected. In the embryonic brain, graphene was localized within the myelin structure and in secondary lysosomes. Graphene induced some atypical ultrastructure and reduced the number of proliferating cell nuclear antigen (PCNA)-positive nuclei and expression levels of PCNA mRNA. The authors suggested that graphene decreased DNA synthesis in the developing chicken brain. The toxic effects of asbestos fibers and CBNPs were also investigated on hepatocytes (Lavrinenko et al. 2016a), with results showing alteration effects on excretory organs of the embryo, causing edema, dystrophy, and formation of calcifications. The increase in the kidney channel epithelium area due to proteinosis and edema of epitheliocytes was statistically proved for both experimental groups.

Lavrinenko et al. (2016b) administered DNPs and carbon nanowires (CNWs) on day 3 of incubation as a suspension of a biocompatible dextran. CNWs caused visual impairment during embryogenesis that began in the early incubation period, while DNPs manifested gradual deterioration of the embryo's condition with the manifestations of the pathology in the temporary organs and the body of the embryos. The results of this study demonstrated that both types of nanostructures can cause sublethal and irreversible morphologic changes. DNPs thus caused vacuolization of mitochondria, and the CNWs caused deformation of their shape and appearance of dark inclusions in them. Lara-Martínez et al. (2017) investigated the toxic effects of functionalized multi-walled CNTs (fMWCNTs) and functionalized oxygen-doped multi-walled CNTs (fCOxs) using a chicken embryo model; results demonstrated severe embryotoxicity in chicken embryos treated with fMWCNTs, while fCOxs seem to exert cardio-embryotoxicity and discrete teratogenicity. Zinabadinova et al. (2018) injected carbon black (soot) and asbestos into the yolks of chicken embryos on the third day of incubation, and showed that the introduction of carbon black and asbestos caused underdevelopment of embryos and vessel depletion in blood islands of the yolk sac. Soot particles disrupted vessel integrity and led to extravasation. The effects of soot were manifested in damage to the blood circulatory system and structural disorders on a cellular level. Samak et al. (2018) recently found that CBNPs induced oxidative stress through an increase in lipid peroxides and decreased glutathione and whole antioxidant capacity concentrations, as well as catalase activity in brain tissues. mRNA transcript levels of antioxidant genes indicated up-regulation of superoxide dismutase-1 and heme oxygenase-1, with notably diminished regulation of glutathione S-transferase-α expression. At the molecular level, with regard to pro-inflammatory genes, interferon-γ was down-regulated, while nuclear factor-κB1 was highly expressed. Also, differences in the expression of apoptotic markers were clearly observed; for instance, caspase-3 and -8, B-cell CLL/lymphoma 2, and cytochrome c were observed at several levels, while up-regulated expression of caspase-2 was found only at higher levels. Together, these findings illustrate that CBNP exposure-mediated overproduction of free radicals, principally at higher concentrations, contributes to inflammation and subsequent cellular apoptosis at the gene expression level, thus revealing a likely molecular association between CBNPs and genes linked to the apoptotic, inflammatory, and oxidant responses.

Using various types of carbon nanoparticles (DNPs, placebo, graphite NPs, pG, large GO, small GO, and rGO) at a level of 500 $\mu g\ ml^{-1}$ injected into the albumin of fertilized chicken eggs, Kurantowicz et al. (2017) showed that reduced embryo survival was affected by the various types of carbon nanoparticles, except DNPs. These results showed that the various types of CNPs can remain in the blood circulation without any major side effects, suggesting their efficient application as a vehicle for active compounds or drug delivery (Kurantowicz et al. 2017). These results are in agreement with those of Szmidt et al. (2016), who studied the toxicity of three forms of graphene: GO, pG and rGO at different levels (50, 500, and 5000 $\mu g\ ml^{-1}$) using chicken embryos as a study model. They found that survival of embryos diminished considerably after contact with all types of graphene, but not in a dose-dependent manner. The body and organ weights were only slightly altered from the highest doses of graphene. The liver function, as represented by 8-hydroxy-2′-deoxyguanosine (8-OHdG), decreased significantly after pG and rGO treatments.

How to cope with nano-carbon toxicity?

Although it is well known that NPs, especially CNPs, readily accumulate within the tissues of the body, their interactions are still known. The effects of NPs on embryonic development or toxicity are critical points because of their potential transport via the placental barrier, and NPs may also cross the BBB

during fetal development and cause neurobehavioral alterations. Given the ability of NPs to penetration various tissues or organs, their long life span, and their circulation, it is important to understand the ultimate effects of these particles in order to mitigate harm or optimize their application. In most instances, the significant effects of NPs can be attributed to small differences in their size, structure, and chemical composition, along with influences on the biological properties of the materials produced as well as on the mechanisms and level of organismal or cellular response.

The production and use of nanomaterials must be regulated for the purposes of sustainability and safety. Thus far, no international standards have been established for the production, use, and commercialization of nanomaterials. However, a few countries have created registries to manage nanomaterials within a commercial profile in their regions. CNTs have been extensively examined and applied in catalytic materials, electronics, biological medicine, environmental engineering, and other related fields (Chen et al. 2014; Lee et al. 2014), and consequently used in several areas including consumer products and industrial applications. Global production of CNTs amounts to 100–1000 tons per year (Piccinno et al. 2012). With the ever-growing application of CNTs, their increased level in the environment will cause a range of ecological problems (Petersen et al. 2011; Jackson et al. 2013). With regard to the safety of nanomaterials in different environments, much biological toxicity has been evaluated; as reported previously, NP toxicity is largely linked to their size, functional groups, structure, and mechanism of exposure (Fabian et al. 2008; Ong et al. 2016). Over time, it is believed that CNTs can accumulate in the tissues and cause inflammation or functional disorders. Thus, the toxic effects of CNTs may be reduced or eliminated through the expulsion of the accumulated NPs from the biological parts of the body as well as treatment of inflammatory or other disorders.

Because airborne NPs are similar to gas molecules, protective measures recognized as appropriate for gases should also work to protect workers from exposure to NPs. Control banding including safety and protection devices and personal protective equipment may be a suitable guideline for workplaces that deal with nanomaterials (Maynard et al. 2007; Schulte et al. 2008). It may be difficult for workers themselves to determine whether they are directly affected by CNTs when working in the production of nanomaterials; therefore, it is important to avoid exposing workers to any airborne NPs (Van Broekhuizen et al. 2011). Investigations aimed at reducing the emission of CNTs into the microenvironment have indicated the need for protective measures in handling operations and work processes such as enclosures, drawbenches, fume cabinets, and local exhaust systems (Methner 2008). Two recommended approaches were established to reduce the emission of NPs into the production environment: First, all areas in which procedures employing NPs are used should be enclosed, and these enclosures must adequately contain gaseous materials. Second, protection and safety measures that are generally effective against dust are also appropriate for the expulsion of NPs and ultrafine particles (IFA 2018). If implementing the above techniques is difficult, local processes such as exhaust ventilation with particulate filters (e.g. HEPA) should be employed, along with personal protective equipment (protective gloves, respiratory equipment, safety shoes, protective clothing, etc.) (Methner 2008). There are steps to elimination controls and safeguarding workers from the harmful effects of carbon nanostructures and CNTs (Grodzik et al. 2013), with the use of personal protective equipment including respiratory protection, protective clothing, and protective gloves constituting the main step. Respiratory protective devices provide the best defense, as a half-mask with a class FFP3 filter class can also be indispensable, and disposable gloves made of nitrile seem to be appropriate for work with NPs (Van Broekhuizen et al. 2011).

Protective clothing should preferably be made of membranous materials and prevent dermal exposure, as knitted or woven fabrics and fabrics made of wool or cotton offer less defense (IFA 2018). Although the effectiveness of protective clothing has not been fully elucidated, some standards have been established, which may be helpful for workplace safety planning (Schulte et al. 2008) An essential process in the manufacture and use of NPs (Van Broekhuizen et al. 2011) is regular cleaning of the workplace, and it seems that vacuuming is an effective and easy cleaning method. In addition, prompt cleanup of any leaks or spill in the workplace is imperative. Suitable special protective gear should be constantly employed during cleaning and maintenance work. Regarding waste management for CNTs, as noted by Ren et al. (2011), CNT waste must be categorized and labeled as extremely harmful, and it must be carefully contained using double-layered polyethylene bags. Proper ventilation, such as local exhaust ventilation with HEPA filters (fume cabinet), is critical. The burning of waste containing CNTs is preferred, as pyrolysis above 500 °C oxidizes CNTs completely.

Conclusions and recommendations

With the ubiquitous presence of nanotechnology, there is a growing likelihood of exposure to engineered NPs, which are associated with harmful or negative effects on health. Results of multiple reports indicate that production of ROS may have a crucial role in CBNPs-induced toxicity; however, to date, the exact molecular mechanism of the toxicity has not been elucidated. In this work, the role of inflammation, apoptosis pathways, and oxidative damage in CBNP-induced neuronal toxicity following in vivo exposure of chicken embryos was revealed. The high generation of ROS or free radicals via CBNP exposure mainly at higher levels contributes to

inflammation and consequent cellular apoptosis at the level of gene expression, thus revealing the potential molecular connection in the middle of CBNPs, and genes related to the oxidant, inflammatory, and apoptotic responses.

Future studies on postnatal exposure to CBNPs need to focus on molecular pathways with frequent long exposure period to experimental period. Studies on CBNP exposure with different routes of exposure should be carried out in the future to establishes strategies for addressing environmental toxicity. The present review also discussed graphene and DNPs and CNTs. Future studies on the main route of exposure to CBNPs as an investigative comparative study using other models, such as rat or mice models, are required.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests with regard to the manuscript.

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