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Application of quantum dots in brain diseases and their neurotoxic mechanism

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The early-stage diagnosis and therapy of brain diseases pose a persistent challenge in the field of biomedicine. Quantum dots (QDs), nano-luminescent materials known for their small size and fluorescence imaging capabilities, present promising capabilities for diagnosing, monitoring, and treating brain diseases. Although some investigations about QDs have been conducted in clinical trials, the concerns about the toxicity of QDs have continued. In addition, the lack of effective toxicity evaluation methods and systems and the difference between *in vivo* and *in vitro* toxicity evaluation hinder QDs application. The primary objective of this paper is to introduce the neurotoxic effects and mechanisms attributable to QDs. First, we elucidate the utilization of QDs in brain disorders. Second, we sketch out three pathways through which QDs traverse into brain tissue. Ultimately, expound upon the adverse consequences of QDs on the brain and the mechanism of neurotoxicity in depth. Finally, we provide a comprehensive summary and outlook on the potential development of quantum dots in neurotoxicity and the difficulties to be overcome.

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1. Introduction

Quantum dots (QDs) technology dates back to the mid-1970s when Dr Brus accidentally discovered that cadmium sulfide displays different colors as the particle size changes.[1] After this, in-depth research on quantum dots was started, and it was found that they have excellent optical properties, such as tunable fluorescence properties,[2] good photostability,[3] small size,[4] and simple synthesis processes.[5] Until P. Alivisatos *et al.*[6] used quantum dots to label fibroblasts in 1998, quantum dots had come a long way in their synthesis, modification, and applications.

Quantum dots exhibit various varieties and predominantly manifest as core–shell structures. Initially, binary quantum dots predominantly consisted of heavy metal ions, such as cadmium-based[7] and silver-based QDs.[8] However, advancements in technology have led to the emergence of non-metallic quantum dots, including silicon-containing QDs (SiQDs),[9] carbon-containing QDs (CQDs),[10] graphene-containing QDs (GQDs),[11] *etc.* There has been a growing development of ternary quantum dots, such as $CuInS_2$[12] and CdZnSe.[13] In addition to altering the composition of QDs, researchers also modified diverse ligands on their surfaces, aiming to improve bioavailability and diminish side effects. These modifications are tailored to meet the specific demands of different applications, such as cell labelling and tracking,[14] deep tissue imaging,[15] theranostics,[16,17] biosensors,[4] and drug and gene delivery.[18] Specifically, the small size of QDs, typically ranging from 2 to 20 nm, allows them to penetrate the Blood–Brain Barrier (BBB),[19] thereby presenting a novel avenue for the manufacture of functional brain probes utilizing QDs.

Despite the proven advantages of quantum dots, concerns about potential toxic effects have always accompanied them. QDs can be transported to different tissues and organs upon exposure, resulting in adverse effects in organisms.[20] This review aims to gather information on recent advancements in applying QDs for identifying and treating brain diseases. It also provides an overview of the pathways through which QDs enter the brain and their interactions with the nervous system. Additionally, it elucidates the mechanisms underlying the toxic effects of QDs within the cerebral nervous system.

2. Application of quantum dots in brain diseases

With the rapid aging of the population and lifestyle change, the incidence of neurological diseases, such as brain tumours, cerebrovascular diseases, and neurodegenerative diseases, continues to rise, placing a heavy burden on health and socio-economic development.[21,22] However, due to the brain's complex structure, almost all neurological diseases lack effective diagnosis and therapy methods in the clinic. Medical imaging techniques or pathological methods commonly used in clinical practice are mainly focused on anatomical and functional changes in organs, with limited help in the early

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diagnosis of diseases. Various physiological barriers prevent drugs from entering the brain. There is an unmet need to formulate new methods for early diagnosis and real-time tracking of the prognosis of CNS disorders. The unparalleled ability of tissue penetration (a few centimeters), spatial resolution (~10 mm), as well as the capability to act as drug carriers make QDs ideal candidates to break through the above dilemma.

2.1. Brain tumours

The overall survival of patients with brain tumours is usually less than 5 years.[23] The earlier diagnosis always indicates a better prognosis. Therefore, developing a highly sensitive and selective diagnostic reagent for detecting brain tumours is urgently needed. QDs can emit iridescent fluorescence and target different cells by modifying various molecules and proteins, making them ideal for visualizing and tracking molecular processes within the cell.[24] More importantly, the feature of QDs penetrating the blood–brain barrier[25] makes it possible to monitor tumour development and neovascularization in real time. Some studies have confirmed the potential of QDs in tumour diagnosis and treatment. Ganganboina *et al.*[26] well-crafted a dual functional probe, S-GQDs@Au–CNS nanocomposites decorated with Angiopep-2, for glioma cell detection. The probe has an excellent linearity range, from 100 cell per mL to 100 000 cell per mL, and the threshold detection limit is 40 cell per mL for detecting glial cells in human serum *in vitro*. In addition to creating a new diagnostic tool, QDs can also be coupled with existing diagnostic methods to improve the accuracy and sensitivity of brain tumor diagnosis. Chunyan Li *et al.*[27] synthesized a unique Gd-DOTA doped Ag_2S QD nanoprobe, which showed an outstanding contrast enhancement in deep tissue imaging, and moreover revealed a high signal-to-background ratio and high spatiotemporal resolution of fluorescence imaging in the NIR-II of Ag_2S. Due to concerns about the toxicity of Gd, the boron-doped graphene quantum dot was a choice for Gd-containing contrast agents. It showed a better T1 contrast enhancement in imaging *in vivo* and was demonstrated to be transported to the brain.[28]

Over and above being a nano-diagnostic tool, the potential of QDs in brain tumour therapy is equally fascinating. The most effective treatment for brain tumours is surgery. Traditional organic fluorophores have limitations distinguishing tumours adjacent to eloquent brain regions, leading to incomplete surgical resection and residual micro lesions.[29] Remnants of microscopic lesions postoperatively constitute a significant cause of tumour recurrence and poor prognosis. Thus, accurate determination of the boundary between malignant neoplasm and normal tissue and identification of micrometastatic tumor cells are essential considerations for complete resection and a critical factor in preventing glioma recurrence.[30] Donna *et al.* employed QDs-EGF and QDs-EGFR as staining agents for glioma cells, tumour bearing mice, and human brain glioma sections. They found a visible distinction between normal and tumour tissue.[31]

Due to the obstruction of the BBB, how to deliver drugs across the BBB and target the tumor tissue are two obstacles to glioma treatment. Due to their small size, quantum dots can serve as vehicles delivering anti-tumor drugs, such as epirubicin, temozolomide, and gemcitabine.[32,33] At the same time, they can control the drug release[34] and increase the concentration of anti-tumour drugs at the tumour site while reducing their concentration in the systemic circulation. Li Z. *et al.*[35] synthesized an Nd^{3+} ion-ligated black phosphorus quantum dot that could penetrate the BBB, monitor the growth of glioblastoma in real-time, and participate in tumour treatment as a photodynamic chemotherapy synergist under specific X-ray guidance. In addition to directly killing tumour cells, quantum dots also have a synergistic effect with chemotherapy, so chemotherapy can play an anti-tumour role at a lower dose level, which is conducive to reducing chemotherapy toxicity.[36] Here, we summarized the applications of QDs in brain tumours in Table 1.

2.2. Cerebrovascular diseases

Cerebrovascular disease refers to cerebrovascular lesions caused by various reasons or brain dysfunction caused by blood flow disorders, including ischemic cerebrovascular disease and hemorrhagic cerebrovascular disease, which is one of the major factors leading to death.[50] Real-time visualization of the cerebral vasculature *in situ* is essential for curing cerebrovascular disease. QDs have a range of superiorities in fluorescence imaging, high tissue penetration depth, good resolution, and rapid data acquisition,[51] which can be applied to non-invasive vascular visualization and continuous monitoring. Jun Q. *et al.*[52] performed bilayer modification of PbS/CdS QDs, which showed high biostability and pH stability, and were successfully used for deep cerebral angiography in mice. In addition to their fluorescence effects, QDs have a sensitization effect to enhance the luminescence efficiency of other fluorescent nanomaterials. Lanthanide-doped nanomaterials (LnNCs) are some of the NIR-II nanoprobes. The sensitizing effect of QDs can increase the brightness of LnNCs by more than 100 times, and their penetration depth reaches 11 mm.[53] The probe can be used for cerebral vascular structure imaging of ischemic stroke and traumatic brain injury and to monitor cerebral vascular hemodynamics. The material is expected to be helpful in pre-hospital diagnosis or early detection of ischemic stroke and in-hospital monitoring of this condition. Here, we summarized the applications of QDs in cerebrovascular diseases in Table 2.

2.3. Neurodegenerative disorders

Neurodegenerative disorders (NDs) are a class of diseases in the brain and spinal cord which are characterized by loss of synapses and neurons. Most research focuses on AD and PD. Some hypothesis had been proposed to explain the pathogenesis of NDs, like oxidative stress,[57] mitochondrial dysfunction,[58,59] immune inflammation,[60] metal ion disorder,[61] and so on, and among them the amyloid cascade hypothesis is the most famous. Due to the complex pathogenesis of NDs, there are very few approaches that have been approved.

Table 1 Application of QDs in the diagnosis and treatment of brain tumours[a]

No.	Core	Shell	Modification	Size	Model	Uses	References
1	InP	ZnS	PEGNIO MIONs Tf	178.5 nm	U87 cell line	Enhanced MRI imaging effect of glioma	37
2	CdSe	ZnS	Interleukin-13	15–20 nm	U251, T3691, and T387 Brain tumour patients' cerebrospinal fluid	Facilitated the early detection of tumor recurrence, distinguished recurrent tumors from pseudoprogress, and potentially enabled the diagnosis of patients in high-risk populations	38
3	$CuInS_2$	ZnS	BSA-DTPAGd Anti-CD133 monoclonal antibody	45 nm	SU2 stem cells Nude mice	Specifically target the tumor cells and enhance the efficacy of contrast agents of MRI imaging	39
4	QD800	—	EG2-hFc EG2-Cys		U87MG.EGFRvIII U87MG.EGFRvIII bearing mice	Non-invasive imaging of brain tumours *in vivo*, detection of tumour aggressiveness and resistance	40
5	$AgInS_2$		CMCel	AIS-CMCel: 3.5 ± 0.5 nm	HEK 293T	Bioimaging and biolabeling in glioma cells	41
			CMCel-Cys	AIS-CMCel-Cys: 3.3 ± 0.4 nm			
			CMCel-PolyArg	AIS-CMCel-PolyArg: 3.7 ± 0.5 nm	U-87 MG cells		
6	Carbon dots	—	Nitrogen	~2.6 nm	293T cells BBB model	Intracellular bioimaging and transfer of the BBB	42
7	$AgInS_2$		CMC-KLA CMC-cysteine CMC-CYS-KLA	—	U87 MG Chicken eggs	Imaging and cellular tracking in U-87 MG cells Inhibited the formation of the new blood vessels in CAM assays	43
8	Gold QDs		—	<10 nm	T98G cells, U87 cells, U373 cells, SNU-80 cells, H460 cells, MRC5 cells, and HEK293 cells	Inhibit self-renewal of tumour cells and reduce tumour metastasis	44
9	Graphene QDs		NH_2– COOH– Green–	10 nm	U87 cells Mouse cortical neurons	Green-QDs and COOH-GQDs serve as synergistic agents with doxorubicin on U87 cells	45
10	CdSe	ZnS	Biotinylated aptamer	20 nm	U87 cells, HUVEC cells, and U87-EGFRvIII cells Nude mouse	Brain tumour imaging in cells and surgical guidance in tumour-bearing mice	46
11	CdSe	ZnS	Liposomes, superparamagnetic iron oxide nanoparticles	CdSe/ZnS: ~8 nm	C6 cells	Surgical guidance and delivery of antineoplastic drugs	47
			Cilengitide	QSC-Lip: 100 ± 1.24 nm	Glioma-bearing rats		
12	ZnCdSe	ZnS	c(RGDyk)-poloxamer-188	212.4 nm	C6 cells, HUVECs, and PC12 cells	Targeting and biolabeling C6 cells *in vitro*, and accumulation in glioma tissue in orthotropic tumour rats	48
					Orthotropic tumour rats	Surgical guidance of glioma	
13	Graphene QDs	—	Nitrogen and boron	~4.7 nm	SF-763 cells, 4T1 cells, and B16F10 cells Nude mice Glioma-bearing nude mice	Visualization of blood vessels and organs *in vivo*. Used as a photothermal therapy agent in the treatment of tumours	49

[a] Abbreviations: MIONs, magnetic iron oxide nanoparticles; PEGNIO, polyethylene glycol niosome; CMCel, carboxymethylcellulose; CMCelCys, carboxymethylcellulose with L-cysteine; CMCelPolyArg, poly-L-arginine with carboxymethylcellulose; BSA-DTPAGd, DTPA-coupled BSA with Gd^{3+} chelation; c(RGDyk), cyclic arginine–glycine–aspartic acid short chain polypeptide.

Table 2 Application of QDs in the diagnosis and treatment of cerebrovascular diseases

No.	Core	Shell	Modification	Size	Model	Uses	Disease name	References
1	PbS	Ag_2Se	V&C	~150 nm	HUVECs cells BALB/c mouse	Early detection of ischemia stroke	Stroke	54
2	Ag_2S	—	V&A	39.4 nm	Brain-injured mice	Early real-time assessment of traumatic brain injury	Traumatic brain injury	55
3	CdSe	ZnS/ZnS	mPEG-PAEA-DDA	—	Cerebral ischemia rats	Detect cerebral ischemic disease in rats	Cerebral ischemia	56

With the development of nanotechnology, many studies have found that quantum dots seem to have potential for the diagnosis and treatment of NDs. QDs can scavenge free radicals effectively, such as superoxide anions, hydrogen peroxide, and hydroxyl radicals. GOQDs exert broad-spectrum antioxidant activity to relieve apoptosis and alleviate α-synuclein and mitochondrial damage in MPP+-treated zebrafish.[62] Once inside the brain, SeQDs can play a similar catalase activity; they can rapidly attenuate AD, significantly ameliorate memory impairment, and improve the learning and memory capacity of AD mice.[63] Beyond that, QDs also achieve some progress in the diagnosis and treatment of Parkinson's disease. GQDs inhibit α-syn fiber formation and trigger fiber depolymerization, promote neuronal and synaptic regeneration, reduce the formation of Lewy bodies and Lewy synapses, promote mitochondrial repair, and prevent interneuronal transmission of α-syn pathology.[64] GQDs could enter neural stem cells *via* endocytosis without altered viability, metabolic activity, proliferation, and differentiation potential in human neural progenitor cells.[65] These studies provide new possibilities for the treatment of neurodegenerative disorders using QDs. Here, we summarized the applications of QDs in neurodegenerative disorders in Table 3.

3. The primary way for QDs to enter brain tissue

Due to the brain's complex structure, traditional delivery methods make it difficult to transport drugs to lesion locations. Nevertheless, the ultra-small size of quantum dots makes them uniquely useful for drug delivery. Studies have shown that QDs can enter the central nervous system through various pathways, *e.g.*, blood–brain barrier, nasal–brain transport, cerebrospinal fluid pathway, *etc.* Some quantum dots are synthesized using heavy metals, and brain tissue is susceptible to these substances. Therefore, an in-depth understanding of how quantum dots enter the brain is conducive to developing new diagnoses and treatments of brain diseases. The different ways for QDs to enter the brain are outlined in Fig. 1.

3.1. Transport through the BBB pathway

The blood–brain barrier is a dynamic interface comprised of blood vessels regulating the passage of compounds both into and out of the brain, from internal and external sources. It can self-regulate in response to subtle changes in the brain or blood circulation to maintain the homeostatic environment of the central nervous system.[75,76] Only lipid-soluble molecules with molecular weight <400 Da can break through the BBB.[77] This property is a double-edged sword, protecting the brain from damage while also making it difficult for most therapeutic drugs to work. It seems to be the crux that has hindered the treatments for neurological diseases.

Due to the small size, biocompatibility, long-term stability, and drug delivery capacity, QDs are expected to solve this dilemma. The following pathways endow QDs with the possibility to go through the BBB: (1) endocytosis, (2) passive diffusion, (3) inhibition of efflux pump, and (4) opening of tight junctions between BBB cells. All of these pathways can also exist simultaneously. S. Kato *et al.* intraperitoneally injected CdSe/ZnS QDs coated with captopril into ICR mice. The results show that quantum dots can cross the BBB and reach the brain and brain parenchyma through transcytosis-mediated patterns. At the same time, they determined cadmium concentrations in different brain regions by ICP-MS. The result showed that cadmium levels significantly increased within the olfactory bulb, cerebral cortex, hippocampus, thalamus, and brainstem of mice.[78] Moreover, quantum dots have demonstrated the ability to traverse the BBB model *via* CD13 receptor-mediated transport channels.[79] QDs destroyed the BBB structure by overproduced ROS and damaged membrane phosphatidylserine.[80]

Zhang *et al.* found that CdSe/CdS-PEG-OH quantum dots clustered in various brain regions can be internalized by microglia.[81] After entering cells, most QDs were distributed in vesicles. In contrast, a few were distributed in tubular structures and polyvesicles.[82] CdS QDs induce neuronal and Purkinje cell degeneration and inflammation in rats.[83]

3.2. Nasal–brain pathway

Intranasal administration is a viable, non-invasive method of intracranial administration. Instilled or inhaled drugs spread across the nasal mucosa and reach the central nervous system through the respiratory epithelium pathway or olfactory epithelium pathway.[84] Studies have shown that ultrafine nanoparticles (<50 nm) are more likely to invade the brain in this way.[85] CdTe QDs went into the nasal cavity of mice and diffused into the olfactory bulb, and nasal fluorescence intensity gradually declined after 2 h. At 24 h, the fluorescence in the olfactory bulb decreased, but the fluorescence was observed in the brain tissue.[86] These results indicate that QDs were transported across the nasal mucosa *via* the axons of the olfactory neurons to the olfactory bulb and distributed throughout the olfactory bulb

Table 3 Application of QDs in the diagnosis and treatment of neurodegenerative disorders

No.	Core	Shell	Modification	Size	Dosage	Model	Uses	Disease name	Hypothesis	References
1	CQD	—	GSH	4.37 ± 0.87 nm	250 μg mL^{-1}	Human serum	Monitoring treatment efficacy and prognosis of PD by testing levodopa	Parkinson's disease	Dopamine theory	66
2	GQDs	—	PEGylated biotin	—	1 μg mL^{-1} in cells 50 μg in mice	Primary cortical neuron cells and C57BL/6 mice	Treat PD by inhibiting α-synuclein (α-syn) fibrillization and disaggregating fibrils	Parkinson's disease	α-syn amyloid aggregation	67
3	CQD	—	Sodium citrate, phenylboronic acid, and 4-aminophenylboronic acid	2–9 nm, 12–22 nm, 5–13 nm	80 μg mL^{-1}	SH-SY5Y cells	Treat PD by scavenging reactive oxygen species	Parkinson's disease	Oxidative stress	68
4	CdSe	—	Mito-metformin	—	30 μg mL^{-1}	N27 cells	Treat PD by reducing mitochondrial dysfunction	Parkinson's disease	Mitochondrial dysfunction	69
5	SeQD	—	—	5 nm	20 μg mL^{-1} 1 mg kg^{-1}	SH-SY5Y cells and AD model mice	Treat PD by scavenging reactive oxygen species	Alzheimer's disorder	Inflammatory, mitochondrial dysfunctions, and oxidative stress	63
6	$CuInS_2$	ZnS	Dopamine	3–5 nm	400 μM	Human serum	Diagnosis of AD by detect ion of tau protein	Alzheimer's disorder	Aβ accumulation, tau protein hyperphosphorylation	70
7	CdSe	ZnS	Biphenyl ethers	5 nm	5–10 mM	PSEN1dE9 transgenic mouse	Treat AD by inhibiting the formation of Aβ fibrils	Alzheimer's disorder	Amyloid hypothesis	71
8	GQDs	—	Glycine–proline–glutamate	18 nm	200 μg mL^{-1}	APP/PS1 transgenic mouse	Treat AD by inhibiting Aβ plaque production and stimulating new neural precursor cells and neuron generation	Alzheimer's disorder	Amyloid hypothesis	72
9	MoS_2 QDs	—	TPP	50 nm	100 μg mL^{-1}	hCMEC/D3 cells, BV-2 cells, PC12 cells, and APP/PS1 transgenic mouse	Treat AD by converting M1 microglia to M2 microglia and clearing Aβ aggregates	Alzheimer's disorder	Amyloid hypothesis	73
10	CNDs B-CDs		Memantine	<5 nm	50 mg mL^{-1}	Zebrafish	Treat AD by inhibiting the aggregation of tau proteins	Alzheimer's disorder	Amyloid hypothesis	74

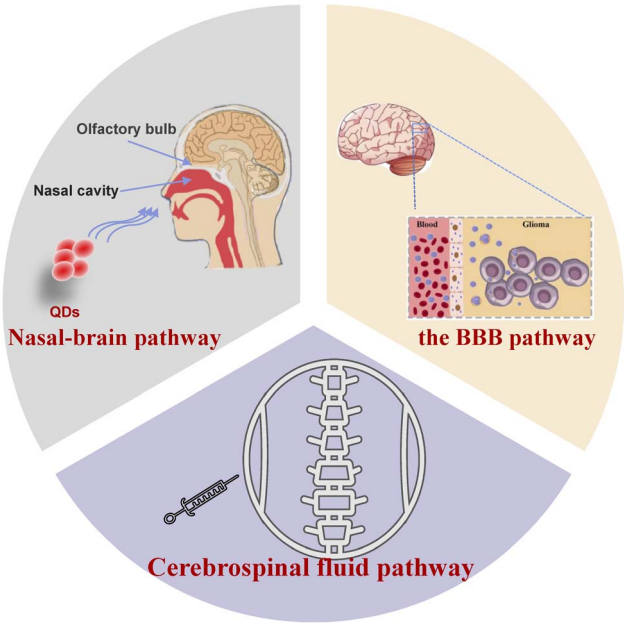

Fig. 1 The different ways for QDs to enter the brain.

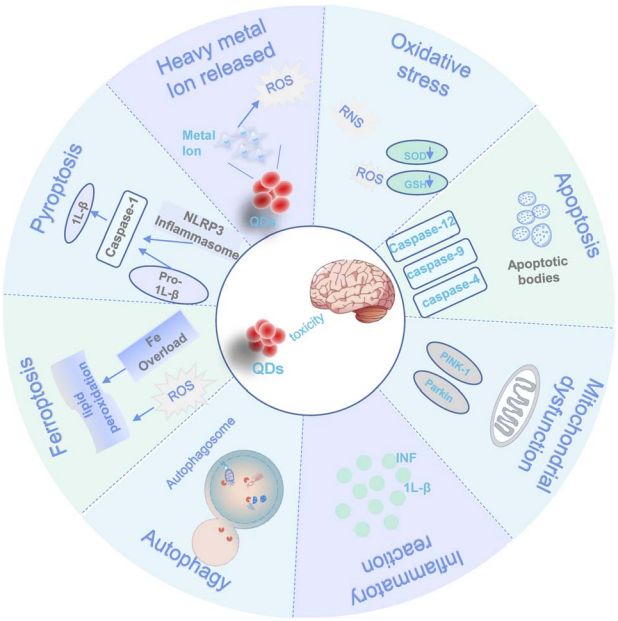

Fig. 2 Schematic diagram of different ways of interaction between quantum dots and the brain.

and the brain. The transportation mode depends on the dimensions and surface modification of quantum dots. When bovine nasal mucosal explants were stained with QDs-COOH and QDs-PEG, respectively, it was found that only QDs-COOH could be detected in nasal mucosal explants.[87] The nasal–brain route can avoid general circulation and reduce systemic adverse events. However, its delivery efficiency is not high, and the drugs that can reach the target lesions are extremely limited, so overdose or repeated doses are required to achieve therapeutic effects. The direction of future research will be how to improve transportation efficiency and reduce the local toxicity of the nasal cavity.

3.3. Cerebrospinal fluid pathway

In addition to the BBB pathway and the nasal–brain pathway, drugs can also reach brain tissue through the cerebrospinal fluid pathway. Moreover, the cerebrospinal fluid pathway allows the rapid distribution of drugs in the cerebrospinal fluid[88] to achieve effective concentrations while simultaneously avoiding the adverse effects of large intravenous doses and effectively increasing the intracerebral concentration of the drug. In order to validate the targeting of brain tissue and the imaging role of QDs in a nude mouse model, Liang *et al.*[89] injected folic acid-modified CdSeTe/Zinc Sulfide (ZnS)QDs into the orthotopic U87MG nude mice transplanted model *via* intrathecal injection. After coupling with folic acid, CdSeTe/ZnS QDs penetrate the tumour interior and potentially contribute to the detection and management of cancer, including image-guided surgery. Juan A. Varela *et al.*[90] performed two types of injections in different cerebral hemispheres of the same rat. At 3 hours after QD administration, massive activation of microglia in cerebral hemispheres injected with localized brain tissue indicated phagocytosis of microglia within the brain within the QDs, and few QDs were observed outside of microglia. In contrast, brain tissue injected into the ventricles did not show microglia activation, and most of the QDs were scattered throughout the tissue. These results suggest that utilization of the cerebrospinal fluid pathway is more conducive to quantum dot distribution within intracerebral tissues.

4. Neurotoxic effects and the mechanism of QDs

With the gradual use of quantum dots, the controversy about the toxicity of quantum dots has never stopped. The toxicity of QDs depends on the size, surface charge, concentration, surface modification, character, and solubility of the materials, as well as the purity.[91–93] There needs to be more comprehensive analyses of the mechanism of QD-induced neurotoxicity. The different ways of interaction between quantum dots and the brain are outlined in Fig. 2.

4.1. Neurobehavioural impairments and brain tissue damage

Neurotoxicity can impair neurological functions and endanger human motor coordination, learning ability, and cognitive functions. Exposure to CdSe/ZnS QDs reduced hatch and survival rates and delayed long development with fertilized zebrafish germ cells.[94] It allows zebrafish to spend more time in dark areas while reducing motor activity in the dark. These changes may result from the alteration of dopaminergic in developing larvae.[95] Prolonged exposure to 0.1–1 g per L CdTe QDs can cause entry of REM motor neurons *via* the intestinal barrier, leading to altered REM development and abnormal foraging behavior in nematodes.[96] In addition, it has been found that QDs decreased the body bends and head trash

frequency and negatively impacted learning and memory ability in *Caenorhabditis elegans*.[97] The same results were observed in the rodent model. Wu *et al.*[98] found that CdTe QDs can decrease Wistar rats' spatial memory capacity; moreover, the short-term memory impairment was dose and time-dependent.

After entering the body *via* the gastrointestinal tract, skin, and respiratory tract, QDs are rapidly distributed throughout the kidneys, liver, lung, gastrointestinal tract, and other tissues and organs with blood circulation.[99–101] They can also cross the blood–brain barrier and enter the cerebral cortex, hippocampus, cerebral nuclei, cerebellu, and other brain regions.[102] The nasal drip of N-GQDs caused decreased organ coefficients and pathological structural damage in rat brain tissue.[103] Prasad *et al.*[104] found that after long-term exposure of CdTe QDs to differentiated PC12 cells, quantum dots were deposited in the cytoplasm. CdSe/ZnS QDs induce autophagosome formation in primary neuronal cells, which triggers autophagy in neuronal cells and results in impaired synaptic function in area CA1 of the hippocampus.[105] CdS QDs injected intraperitoneally into mice for one week caused vascular atrophy, congestion, and degeneration in the brain and cerebellar tissue, necrotic degeneration, and DNA breaks in neurons and astrocytes in cortical regions, and pathologic features such as reduced Purkinje cell number and size, cellular degeneration and apoptosis.[83]

4.2. Mechanism of neurotoxicity induced by QDs

Several mechanisms contribute to the neurotoxicity of QDs. They mainly include non-neurological specific mechanisms (*e.g.*, such as oxidative stress, heavy metal ion release, apoptosis, mitochondrial dysfunction, inflammation, autophagy, ferroptosis, pyroptosis, and genomic instability.) and neurological specific mechanisms of action (*e.g.*, intervention in GABA metabolic pathways and neurotransmitter receptor-mediated). An overview of the non-neurological mechanisms of QDs is provided in this review. Table 4 demonstrates some neurotoxicity mechanisms in QDs.

4.2.1. Oxidative stress and energy depletion. The Förster resonance energy transfer (FRET) mechanism allows QDs to be used for the photodynamic therapy of tumours.[118] In the next generation of photodynamic therapy, photosensitive drugs afford energy to oxygen molecules, producing excited oxygen – singlet oxygen, which is highly active and can kill tumor cells by producing cytotoxic effects. It has been shown that QDs can cause DNA strand breaks by binding to plasmid DNA labeled with photobiotin by the light-activated DNA strand.[119] QDs induce the production of ROS, which can cause brain diseases *in vivo*, such as Alzheimer's disease.[120] Studies have shown that QDs can cause oxidative stress through various pathways: (1) direct production of ROS through their physicochemical properties, (2) indirect production of ROS and reactive nitrogen species (RNS) through stimulation of inflammatory cells, (3) production of ROS through the release of ions or soluble compounds.[121] Several studies have shown that cells and tissues exposed to QDs have a significant decrease in SOD and GSH, while ROS levels are high and MDA is increased.[122,123] ROS can disrupt the cellular structure, perturb cellular function, and even lead to cell death. Lovrić J. *et al.*[124] found that both ROS expression and the rate of apoptosis were significantly decreased when the cells were co-treated with the antioxidant NAC *in vitro*, suggesting that quantum dot-induced oxidative stress may be inhibited by antioxidants, further suggesting that the cytotoxicity induced by QDs may be due to ROS generation.

Laurie E. Hopkins *et al.*[125] exposed mice to aerosolized CdSe/ZnS QDs for 1 h. No acute cytotoxicity of the nasal epithelium or olfactory bulb was found, but increased microglia activation in the olfactory bulb of mice exposed to QDs was observed. Microglia are the intrinsic immune cells of the central nervous system and constitute only 5–20% of glial cells. Under stressful conditions, microglia are activated and release anti-inflammatory cytokines and chemokines that reduce the inflammatory response while producing reactive oxygen and nitrogen species. Ren *et al.*,[73] in their exploration of QDs for AD, found that TPP-MoS2 QDs attenuated Aβ aggregation-mediated neurotoxicity by switching microglia from a pro-inflammatory M1 phenotype to an anti-inflammatory M2 phenotype, resulting in the elimination of Aβ aggregation in mice with AD. On the other hand, if overactivated or chronically activated, microglia can lead to further brain injury caused by the release of pro-inflammatory cytokines. After entering microglia, CdTe/ZnS QDs are capable of polarizing microglia towards the M1 phenotype through activation of the mammalian target of the rapamycin (mTOR) protein pathway and activation of Nod-like receptor 3 (NLRP3) inflammatory vesicles to release inflammatory factors TNF-α, IL-1β, and NO, resulting in secondary inflammatory damage.[126] Fuster *et al.*[106] assessed the effects of CdSe-QDs on human T98G glioblastoma cells using RNAseq at maximum noncytotoxic dose. They found that after 72 h of CdSe-QDs exposure, altered signaling pathways primarily involved regulating inflammatory and immune responses and regulating the gonadotropin-releasing hormone receptor pathway, including the NF-κB and MAPK signaling pathways.[127] In addition, $CuInS_2$/ZnS-PE negatively regulates the downstream MAPK cascade, which significantly downregulates the expression of the NGF receptor (p75NTR) and inhibits NGF-induced synaptic growth through the NGF/p75NTR/MAPK pathway,[128] causing neurotoxic damage.

4.2.2. Heavy metal ion release. Heavy metal ions, such as Cd^{2+}, Ag^{2+}, Cu^{2+}, *et al.*, are the most common components of QDs. After entering the body, these ions can be unloaded and released into the circulation. Many factors can affect the release processes of the heavy metal ions such as the synthesis methods, the surface modification, and the extracellular environments. For example, when the Se concentration is increased in the synthesis process, the Cd^{2+} density on the surface of the CdSe QDs will decrease.[129] Furthermore, when exposed to ultraviolet or oxidized, the Cd^{2+} release will increase.[130] The core–shell structure can also influence Cd^{2+} release from Cd-containing QDs. For instance, with the same capping agent, the Cd^{2+} content in CdTe QDs was much higher than that in CdTe/ZnS QDs.[131] Compared with the core/shell structure quantum dots, the biological safety of the core/shell/shell structure quantum dots is superior.[132]

Table 4 Neurotoxicity mechanisms in QDs

No.	QDs	Dose	Exposure time	Model	Toxicity mechanism	Reference
1	CdSe	40 μg mL^{-1}	72 h	T98G human glioma cells	Regulated neuroinflammation *via* hormonal control of the hypothalamus *via* gonadotropin-releasing hormone receptors. Downregulated the pro-inflammatory interleukin gene	106
2	CdS	*In vitro*: 0.01–100 μg mL^{-1} *In vivo*: 0.1–25 mg kg^{-1}	24 h	Cerebellar cell culture and male SD rats	CdS at 0.01 μg mL^{-1} had no significant toxic effect. The expression of 8-OHdG and GFAP was significantly up-regulated at high doses	83
3	MPA-CdTe	0, 20 μM, 40 μM, and 80 μM	24 h	RSC96 cells	The induction of RSC96 apoptosis and autophagy by CdTe QDs was concentration-dependent and could lead to apoptosis and autophagy through the mitochondrial and endoplasmic reticulum pathways	107
4	Ag_2Se	0, 0.01 μM, 0.1 μM, and 1 μM	24 h and 72 h	*C. elegans*	The accumulation of Ag_2Se QD_S in *C. elegans* shortens its lifespan and disrupts its normal neural behavior. In addition, Ag_2Se QDs caused an overproduction of ROS and altered the expression of genes involved in REDOX balance	108
5	Graphene QDs			U251cells	ROS generation and singlet linear oxygen kill U251 human glioma cells *via* autophagy and apoptosis	109
6	$CuInS_2$/ZnS	12.5–100 μg mL^{-1}	24 h	U87 cells	$CuInS_2$/ZnS QDs can enter cells with low cytotoxicity, primarily in the cytoplasm. However, they can cause significant alterations in gene expression patterns, including ribosomes, DNA-chromosome binding, and chromosome assembly	110
7	MPA-CdTe, CdTe@ZnS	BV2 cells:1.25 nM and 5 nM *C. elegans*: 0.01 μM and 1 μM Mice: 0, 0.25 mM, and 2.5 mM	BV2 cells: 12 h *C. elegans*: 24 h, 72 h Mice: 24 h, 28 days	BV2 cells *C. elegans* Mice	In *C. elegans*, exposure to QDs induced immune responses and neurobehavioural deficits. Neuroinflammatory responses to QD exposure, including activation of microglia and release of IL-1β, were observed in the hippocampal region of QD-treated mice. QDs containing Cd activate the NLRP3 inflammasome by inducing excessive ROS production and releasing IL-1β	111
8	MPA-CdTe	10 nM, 20 nM, and 40 nM	24 h	BV2 cells	Exposure to high levels of MPA-CdTe QDs activated microglia, promoted the secretion of IL-1β, and was strongly correlated with activation of the TLR2/MyD88/NF-κB pathway and NLRP3 inflammasome induced by ROS	112
9	CdSe/ZnS-LPS	10 μg mL^{-1}	24 h	N9 cells	LPS QDs induce toll-like receptor 4 (TLR-4) activation and subsequent NLRP3 inflammasome vesicle activation through p38 and JNK signaling. In the inflammasome, pro-caspase 1 is cleaved, and caspase-1 is	113

Table 4 (*Contd.*)

No.	QDs	Dose	Exposure time	Model	Toxicity mechanism	Reference
					released from pre-cleaved IL-1β, ultimately releasing the pro-inflammatory cytokine (IL-1β)	
10	Gold QDs	25 nM	48 h	U373 cells and U87 cells	Gold QDs and cold atmospheric plasma (CAP) induce different glioma cell death through the Fas/TRAIL signal pathway	114
11	CdTe and CdTe@ZnS	1.25 nM, 2.5 nM and 5 nM	12 h	BV2 cells	Both QDs could trigger NLRP3 priming and pro-IL-1β expression, up-regulation in IL-1 β release, ultimately causing cell death by pyroptosis	115
12	Ag_2Se QDs	1.25 nM, 2.5 nM and 5 nM	12 h	BV2 cells	Ag2Se QDs triggered NLRP3 priming and pro-IL-1β expression through the activated NF-κB pathway and ROS generation; these factors all up-regulated in IL-1 β release and then led to pyroptosis in microglia	116
13	MoS_2 QDs	50 μg mL^{-1}	0 h, 4 h, 6 h, and 12 h	Primary microglia Primary astrocytes	MoS_2 QDs promote NLRP3 inflammasome priming, resulting in microglia cell pyroptosis through the caspase-1 signal pathway	117

The concentration of heavy metal ions is a critical factor in the cytotoxicity of QDs.[126] Studies have shown that Cd^{2+} dissociated from CdTe QDs can promote the adverse effects of CdTe QDs.[133] We speculated that the following reactions would occur in cells with QD exposure: CdTe QDs were disassembled by intracellular enzymes and released Cd^{2+}. Cd^{2+} and CdTe QDs induced cells to produce excess ROS together;[121] the excess ROS produced could chemically degrade the CdTe QDs, which resulted in more Cd^{2+} being released from the CdTe QDs.[134,135] Besides the toxic effects caused by heavy metals, studies have shown that Cd^{2+} can affect the metabolism of other metal ions, like Cu^{2+} (ref. 136) in organisms, which in turn causes further damage to the body.

4.2.3. Apoptosis in neuronal cells. Apoptosis is the process by which cells automatically terminate their life under certain physiological or pathological conditions controlled by intrinsic genes.[137,138] Apoptosis can occur through various signaling pathways, the core of which is activating a group of intracellular cysteine proteases in response to pro-apoptotic signals.[139] Apoptosis is primarily divided into endogenous apoptosis and exogenous apoptosis. Through the activation of cell surface death receptors such as (Fas, TNF R1, *etc.*), the exogenous pathway results in the activation of caspase-8 or caspase-10 (ref. 140) as well as the endogenous pathway *via* the release of cytochrome C from the mitochondria and associated activation of caspase 9.[141] In addition, there is an atypical pathway activated by various endoplasmic reticulum stress injuries, which also leads to caspase-9 activation.[142] The various pathways to apoptosis are intersected.

4.2.3.1 Cell-surface death receptors. In nucleated cells, the extrinsic pathway of apoptosis is triggered by the interaction of death ligands of the tumour necrosis factor superfamily with the death receptors on the external cell surface membrane, including FAS ligand-FAS/APO1, TNF–TNF receptors, and TRAIL–TRAIL receptors. Co-treatment with AuQDs and CAP induces reactive oxygen/nitrogen species (RONS) that promote apoptosis in tumour cells by positively regulating the expression of the apoptosis-associated Fas signaling pathway in both U373 and U87 cells.[114] NAC and Trolox are two common antioxidants, and Trolox does not have a significant protective effect against the toxicity of the CdTe QDs on PC12 cells. However, it is still being determined how to protect against these effects while NAC can withstand active quantum dot damage on PC12 cells.[124] Thus, NAC may activate the Ras-ERK pathway in PC12 cells,[143] promoting the activation of PC12 cell proliferation and producing an anti-apoptotic effect.

4.2.3.2 Mitochondrial apoptotic pathway. Mitochondria are the main sites of ATP synthesis, providing energy for cellular activities, maintaining intracellular Ca^{2+} homeostasis, controlling aerobic metabolism, and maintaining cell survival.[144–146] Chan *et al.*[147] found that QDs up-regulated BAX, p-MAPK/JNK expression in human neuroblastoma cells and down-regulated BCL2, p-MAPK/ERK, HSP90, RAF1, and RAS protein expression, leading to a loss of mitochondrial membrane potential, mitochondrial release of cytochrome c, as well as apoptosis-inducing effects of caspase-9 and caspase-3 leading to apoptosis. Based on these findings, structural disruption and functional impairment of mitochondria are considered two major factors of quantum dot toxicity. The leading cause of the

endogenous apoptotic pathway is mitochondrial damage, where exogenous or endogenous toxicants enter the cell and block the transmission of the mitochondrial respiratory chain, causing mitochondrial swelling, lowering mitochondrial membrane potential, altering mitochondrial membrane fluidity, inducing the opening of the permeability transition pore (MPT) of the mitochondrial inner membrane, and the release of pro-apoptotic proteins.[148,149] Both pro-apoptotic and anti-apoptotic Bcl-2 family members have been shown to regulate apoptosis by regulating the release of mitochondrial factors, including cytochrome c; the quantum dot-induced apoptosis signaling pathway has also been shown in human neuroblastoma.

4.2.4. Ferroptosis in neuronal cells. Ferroptosis is a new type of programmed cell death that depends on intracellular iron accumulation and redox system disorders.[150] Scientists have tried to explore the correlation between ferroptosis and QDs on various models, and some results have been drawn from it. Liu *et al.*[151] put forward that the Nrf2/ERK signaling pathway was involved in ferroptosis in CdTe QDs. They found that CdTe QDs triggered the Nrf2/ERK signaling pathway, induced the formation of iron phagosomes, and contributed to FTH1 in lysosomes, proteasome degradation, and release of free iron ions, resulting in ferroptosis in macrophage. Neurodegenerative disease development and tumour resistance are inextricably linked to iron dysregulation.[152,153] In the meantime, QDs had been confirmed with the ability to damage the iron metabolism and disturb redox balance in microglia. GQDs caused cytoplasmic iron overload, depletion of GSH, and excessive generation of ROS and lipid peroxidation (LPO) in BV2 cells; the expressions of ferroptosis-related proteins SLC7A11 and GPX4 were significantly decreased. Meanwhile, the expression of ACSL4 and COX2 was increased.[154] For further exploration, L-VGCCs in the plasma membrane and ryanodine receptors are involved in N-GQDs inducing cytosolic iron overload. These two calcium channels can regulate the production of ROS and inflammatory cytokines, leading to ferroptosis and inflammation in microglia.[103] In addition to the adverse effects on the cells, many studies have shown that ferroptosis is related to cancer resistance; thus, regulating the ferroptosis process may be an effective method for cancer treatment. Yao *et al.*,[155] designed creative CQDs modified with chlorogenic acid, which distinctly transformed GSH into GSSG and promoted cell ferroptosis in HepG2. Besides these, the CQDs can recruit the immune cells attacking the tumour cells, which is expected to be used to treat tumours.

4.2.5. Pyroptosis in neural cells. Pyroptosis is an inherently programmed cell death with dual apoptotic and necrotic properties, characterized by activation of the caspase-1 signaling pathway.[156] After pyroptosis was raised in 2001,[157] some researchers explored the relationship between neurotoxicity and pyroptosis and obtained some clues. Wu *et al.*[111] found that Cd-containing QDs can upregulate NLRP3 protein expression and trigger caspase-1 activation in the hippocampus of mice. However, the proteins involved in apoptosis have no change. In the meantime, Z-VAD-FMK, a caspase-1 inhibitor, could protect BV2 cells by restraining caspase-1 activation and reducing the IL-1β production.[115] The same phenomenon was also observed in non-Cd-containing QDs. MoS2 QDs triggered the formation of NLRP3 inflammasome and promoted the release of pro-inflammatory cytokines, triggered caspase-1 activation, and resulted in pyroptotic death in microglia.[117] Nonetheless, pyroptosis of QDs not only brings damage but is also therapeutic. Jiang *et al.*[158] designed a photosensitizer based on carbon dots which will act as a pyroptosis accelerator in tumour cells. When taken up into tumour cells, it can combine with RNA and break down the RNA structure, which induces pyroptosis in tumor cells.

5. Conclusions

Quantum dots have obvious biomedical value. On the one hand, there is a thirst for this advanced technology. On the other hand, there are severe concerns about toxic effects. What lies ahead of the widespread use of quantum dots is a path of continued exploration. QDs cause neurological damage through multiple pathways, and these toxic effects may involve various mechanisms and numerous neural factors. However, the existing studies cannot fully grasp the transformation process and the existing form of quantum dots in the nervous system. Therefore, further studies are needed to focus on the molecular mechanisms of quantum dot-induced neurotoxicity.

Meanwhile, due to the complex structures and functions of the nervous system, most of the studies had been carried out *in vitro*. More *in vivo* studies still need to be performed to predict the toxic effects of quantum dots on humans more accurately. At the same time, evaluating the toxicity and safety of QDs has yet to catch up with their applications. Further understanding of the mechanism of neurotoxicity caused by quantum dots is expected to accelerate the application of quantum dots.

Conflicts of interest

The authors declare no competing financial interest.

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