



Nanotechnology and quantum science enabled advances in neurological medical applications: diagnostics and treatments

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Abstract

The beginning of the twenty-first century saw advancements in all areas of life, including medicine and nanotechnology. This review will look at the most recent advances in nanomaterials for diagnostics and treatments. The emphasis is on the application of nanofibers, nanosensors, and quantum dots (QDs) in medication delivery, neuron regeneration, chemical detection, and microelectrode probes. The manufacture of implantable nanofibers and nanosensors based on QDs, and their application-specific features impacting the interface with targeted brain cells were described. The collaborative efforts have helped us to understand the potential of nanostructured materials in fabrication to overcome the limits of micro and bulk materials in treatments and diagnostics. These advancements will eventually lead to using nanostructures, including nanofibers and nanosensors, in high throughput cutting-edge applications. Only when extensive safety investigations have been completed may the use of nanomaterials on an industrial basis be viable.

Keywords Nanofibers · Biomaterials · Nanosensors · Drug delivery · Quantum dots (QDs) · Neural regeneration · Neuroscience

1 Introduction

Since 1959, when Richard Feynman famously stated, “There is plenty of room at the bottom,” practitioners, technologists, scientists, and researchers have realized the importance of nanotechnology and quantum science in medicine. Nanotechnology is a multidisciplinary field that stands on the shoulders of numerous disciplines, including materials science,

polymer chemistry, and others. This technique works on a one billionth of a meter scale (10^{-9} m). It enables very selective and efficient interactions of nanostructured materials for diagnosis, imaging, and/or medication delivery at the cellular and subcellular levels. As a result, it is critical to shedding light on the erudition of current-state-of-the-art. These materials, which include engineered NPs, micelles, quantum dots, liposomes, nanofibers, and nano scaffolds for neuro disorders, transport drugs to areas that would otherwise be inaccessible [1]. Furthermore, a study led by Johns Hopkins Medicine researchers reports that Norrin protein mutations that cause blindness and other intellectual problems during infancy can be treated with Norrin NPs, stimulating the growth of neural branches in the brain. Such biomolecular interactions occur at the nanoscale, putting a strain on the use of nanomedicines in treating of brain diseases [2].

Nanomaterials not only produce the desired physiological response when they interact with cells, but they also reduce the risk of side effects observed with micro materials. As a result, advancements in biotechnology have played an essential role in treating of neurological disorders by developing advanced and more straightforward methods using nanotechnology. Furthermore, the

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most recent CAGR predicts a 17% increase in the use of nanomedicines by the end of 2022. At the same time, nanomedicines include nanotools used in disease diagnosis, prevention, and treatment, and understanding the underlying phenomena that cause the disorders. The smaller-scale technology (Fig. 1) has also had a significant impact on refining the diagnosis and imaging protocols of various disorders by using nanotubes (1 D), nanofibers (1 D), quantum dots (0 D), nanoarrays (arrays of nanowires), nanoprobes, NPs (diameter from 1 nm to several hundred nm, 0 D), nanochannels, and nanowires (1 D) [3, 4].

The human brain is a dynamic organ, as are its functions and dysfunctions. Such discoveries are unavoidable to unravel information from neural networks in the brain. Similarly, the Nobel Prize in Medicine in 2014 was shared by three people: a Norwegian couple, May-Britt and Edvard Moser, and British-American John O’Keefe, for their invaluable contributions to unravelling the mystery of the brain. They wanted to know how mammals, such as humans, create a map of places in their brain using neighboring hippocampal cells, allowing them to locate pathfinding and accurate positioning [5]. Scientists have been looking for tools for neurosurgical protocols for years. While the use of nanotools is not yet ubiquitous, it is paving the way for neurosurgeons to employ them in the future to restore injured or non-functional neurons.

1.1 Human brain—a part of central nervous system

The brain is the most sensitive and essential portion of the central nervous system (CNS) and the most complicated biological organ on the planet. Neurons are the primary building blocks of the CNS; it is estimated that the brain has 85 billion neurons. Neurons control the muscle response, behavior, memory consolidation, sensory, motor, and intellectual activities of the brain [6, 7]. The first to agree that a human’s mind and intelligence are directed by the brain were Greek philosophers, and later work by Galen and Thomas created the groundwork for neurology. Cajal’s work, on the other hand, advanced these concepts further by introducing neurons and establishing the present-day study of neuroscience

[8]. Since then, much research has gone into understanding inter-neural interactions, which is necessary to determine the origin of malfunction (brain illnesses) and shape our observable behaviors. Physiologic and cognitive disability, cancer, trauma, or any neurodegenerative disease can all be caused by a disturbance in neural circuits. As a result, better knowledge of these neural networks’ functioning is critical for treating brain illnesses [9]. On the other hand, scientists have been working for more than a century to understand brain circuitry, which could be done by photographing neuronal connections in the brain. The absence of chemical and dynamic information due to the spatiotemporal orientation of neurons overlaying memory and learning is a shortcoming of this data. In this regard, in 2013, a collaboration of neuroscientists and nonscientists launched the initiative Brain Activity Map (BAM). Scientists can create technologies for linked ailments if they have a thorough grasp of brain circuitry, which will advance artificial intelligence to the next level. The goal of the study is to learn the brain’s circuitry to artificially imitate it to treat disorders caused by its malfunctioning [10]. Hence, several other medical history initiatives are remarkable results of the fusion of nanotechnology and neuroscience. According to a recent study, surface plasmon resonance of Au NPs may quickly and successfully identify the biomarker UCH-L1 in TBI patients with 100% sensitivity and specificity [11]. Another nanotechnology procedure to address the confinements of light entrance and invasiveness of customary optogenetics is by means of injectable upconversion nanoparticles (UCNPs). Since the absorption of light by organic tissue is wavelength-dependent, the use of molecularly tailored UCNPs that are activated with NIR and emit light in visible range empowers the transcranial deep brain incitement by red-shifting excitation wavelengths. These core-shell UCNPs were coated with silica or poly (acrylic corrosive) to improve their stability and biocompatibility [12]. Apart from the complicated neuronal network, the subtle and well-guarded nature of the brain also poses a challenge in diagnosing and treating it.

The published literature on nanostructures for neurological medical system diagnosis and treatment is extensive. The production, characterization, and uses of nanomaterials,

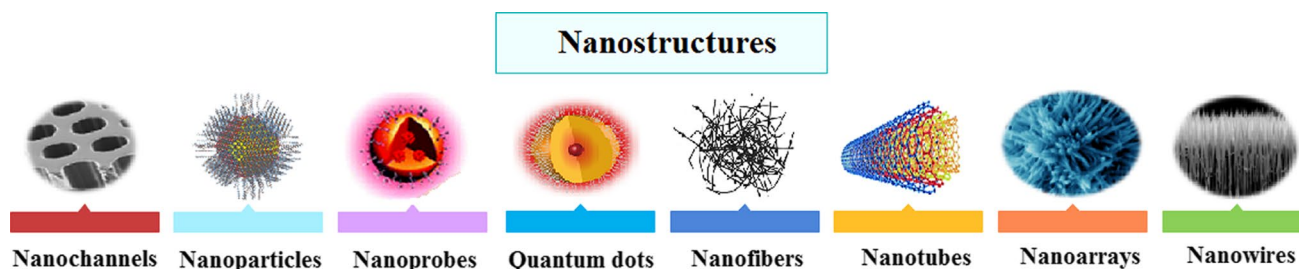
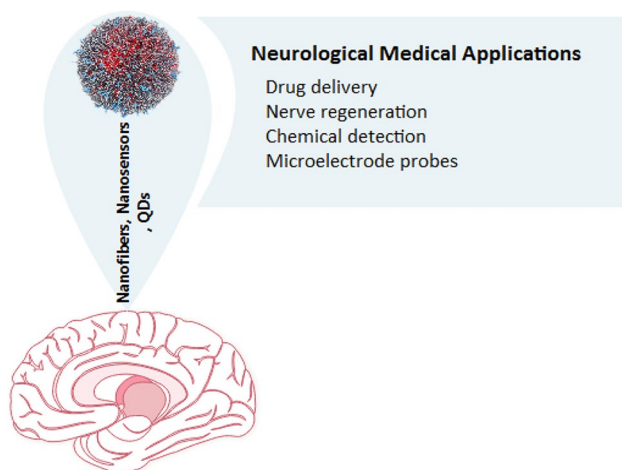


Fig. 1. The morphology of nanostructures with sizes ranging from 1 to 100 nm that can be used in the diagnosis and treatment of CNS diseases



Scheme 1 Nanomaterials and their applications in neurological medical applications

including nanofibers, nanosensors, and quantum dots, in detecting and treating CNS illnesses will be discussed in detail in this study (Scheme 1). In a nutshell, we will talk about the blood–brain barrier (BBB), nanomaterials, and their applications. Finally, a detailed review of the literature covering nanostructure uses in CNS illnesses is presented, followed by conclusions and future prospects for this type of material.

The BBB (Fig. 2) is a primary barrier to the entry of many micro and macromolecules into the brain, and it predicts

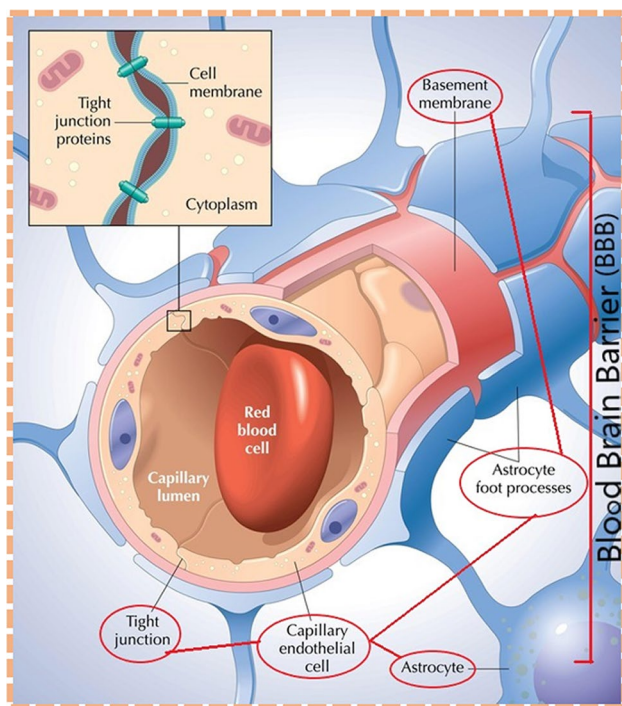


Fig. 2 Schematic depiction of blood brain barrier (BBB) [13]

the efficacy and efficiency of medication interventions in the treatment of diseases like tumors [13]. This selective impermeable membrane allows only glucose, amino acids, oxygen, and other necessary lipophilic substances and tiny molecules to pass through. However, because it avoids the BBB and thus allows for focused drug administration, the nose to brain pathway is a feasible option for medication therapy. Nonetheless, this mode must pay close attention to lipophilicity, high solubility, formulation design, and toxicity of drugs for nasal passage.

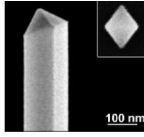


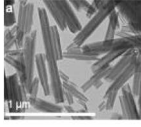
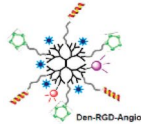
2 Nanotechnology diagnostic tool

Considering all of these impediments, the advent of nanotechnology offers a revolutionary solution due to its small size, lower toxicity, and improved target specificity in drug therapies, diagnosis, imaging, and modeling [7]. Nanotechnology promotes development by utilizing the nanometer scale of materials instead of bulk counterparts, as material properties are enhanced due to a large surface area to volume ratio. Other advantages of nanomaterials include higher reactivity and functionality, fewer side effects, efficient drug delivery, target, and time-controlled release, and surface modification. These characteristics are essential for drug delivery across the BBB due to their small size, controlled and targeted release, and drug robustness. Liposomes, nanogels, NPs, nanofibers (Table 2), and nanotubes are used as nanocarriers in drug delivery [14].

The features of nanoparticles and their uses in diagnosis and therapy are described in Table 1. These biodegradable nanocarriers can carry both lipophilic and lipophobic substances across biological systems. For example, dalargin polysorbed on polybutyl cyanoacrylate-based NPs coated with polysorbate-80 can be transported across the BBB, resulting in a sufficient antinociceptive effect [20]. Similarly, the antibiotic ciprofloxacin was administered by cholesterol and poly (ethylene glycol) PEG-based micelles with a diameter of less than 180 nm [21]. Such polymeric micelles protect drugs from premature release and degradation by providing controlled and sustained drug release via diffusion once they reach the target cells. Similarly, nanogels are being used to deliver cisplatin to treat glioblastoma, a type of aggressive brain tumor. The number of survival days increased when cisplatin-loaded nanogels were administered to model experiment rats. This preliminary demonstration may pave the way for future drug delivery research in treating of lethal gliomas [22]. However, in treating of CNS diseases, the insufficient aqueous solubility of organic molecules is a significant barrier to drug delivery.

Surface modification of NPs with cell-penetrating peptides CPPs can improve nose-to-brain drug delivery by improving transmucosal transport. Furthermore, due to their

Table 1 Some important characteristics of nanomaterials and applications

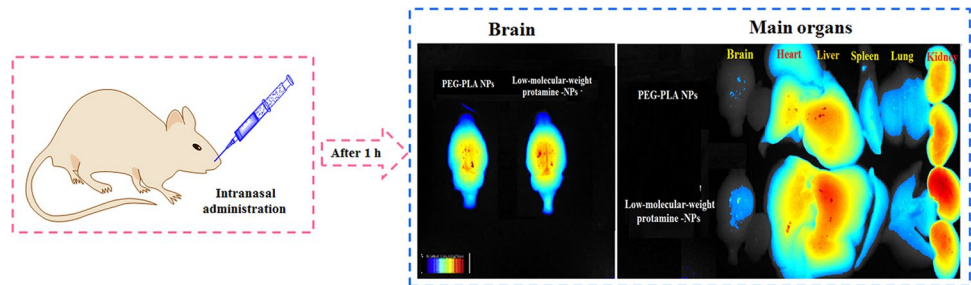
Nanomaterials	Examples	Specifications	Shape	Applications	Ref
Nanowires	Au NW electrodes	Diameter~30-150 nm and length ~100 μ m		Electrode miniaturization; Recording of neural activity	15
Nanoribbons	In ₂ O ₃ nanoribbon field-effect transistors (FETs)	Thickness ~ 16-nm		Sensing of temperature, pH, serotonin, and Dopamine	16
Nanorods	Eu-doped Gd ₂ O ₃ nanorods	Length ~ 90.9 \pm 37 nm		Detection and treatment of glioma	17
Nanotubes	Halloysite nanotubes	Lumen ~ 50 and 60 nm, Diameter ~12–15 nm, Length ~ 500–900 nm		Drug delivery; isothiocyanate and ionomycin into brain microvascular endothelial cells (BMVECs)	18
Nanoprobes	Dendrimer (Den) Cyclic arginine-glycine-aspartic (RGD) tripeptide; angiopep-2/ (Angio)	Diameter ~15.6 nm		Brain tumor imaging	19

high cell translocation and non-mutagenicity, surface modified poly (ethylene glycol)-poly (lactic acid) (PEG-PLA) NPs with low molecular weight protamine (LWMP) act as efficient drug carriers. LWMP-modified NPs are approximately 100 nm in size, allowing them to enter the brain via olfactory neurons. When coumarin-6 was incorporated as a fluorescent probe into LWMP-NPs, brain distribution analysis revealed that CPPS containing modified NPS had a greater distribution than unmodified NPs (Fig. 3). It is thought that medication delivered intranasal diffuses to the CNS via the olfactory and trigeminal neurons, which are aided by LWMP alteration [23]. Similarly, Katare and his colleagues developed a dendrimers-based formulation for intranasal delivery of weak hydrophilic haloperidol to the

brain. Intranasal administration of dendrimer-based formulations produces comparable behavioral reactions at a lower dose than intraperitoneal injections, validating the drug's improved efficiency and controlled release [24].

These and other studies demonstrate the validity of nanotechnology in the treatment of brain diseases. Previously, the nanoimaging tool atomic force microscopy (AFM) was widely used in imaging neurodegenerative diseases, but it is only effective in the early stages of the disease. As the age of compactness has undoubtedly approached all branches of technology, magnetic nanoparticles (MNPs), carbon nanotubes (CNTs), and quantum dots (QDs) are now used as nanoprobes in medicine. As nanoprobes, they can detect, progress, and locate the exact location of a tumor, its

Fig. 3 Optical images of LMWP-NP distribution in the brain and major organs after intranasal administration [23]. Reproduced with permission



margins, and adjacent structures, as well as track the efficacy of a drug administered inside the body. Because of their magnetic properties and ability to cross the BBB, iron oxide NPs are being investigated as potential nanomaterials for magnetic resonance imaging (MRI) [25]. When the size of iron oxide NP is less than 50 nm, the material is referred to as ultra-super paramagnetic (USPION). However, due to their shorter half-life than USPION, gadolinium chelate-based complexes are currently used for imaging in MRI. The longer stability is important in determining the tumor’s diagnosis, as they tend to accumulate in tumor margins, and assessing post-operative conditions based on neurological activity and pharmaceutical therapies [26]. Similarly, gold nanoparticles (GNPs) can be used to record high-resolution brain tumor pictures utilizing synchrotron-based computed tomography (CT), while hydrophilic, biocompatible GNPs coupled with FePt NPs and chelated with gadolinium offer images with the precise position of particles to estimate the optimal irradiation dosage for treatment [27, 28]. Due to its invasive growth and the uncertain border with brain cells, glioblastoma (GBM), a malignant brain tumor of the CNS, is frequently incompletely removed after surgery. Intraoperative brain shifts disrupt the pre-operative anatomy during tumor excision, and the operation accuracy suffers as a result. To circumvent this constraint, a fluorescent 5-amino-levulinic acid was combined with a spectroscopic probe used for GBM resection. Similarly, ZnCdSe/ZnS QDs were employed to perform ultrasound-targeted microbubble

destruction (UTMD) technology-assisted surgery. To create GBM targeted QDs-c(RGDyK)NP, fluorescent QDs were encapsulated by c(RGDyK)-poloxamer-188 polymer NPs. A QDs-based fluorescent probe guided the removal of a glioma tumor, and an evident cavity was produced following the surgery. However, the presence of GBM tumor cells (Fig. 4) highlights the value of real-time imaging for precise surgery [29]. The role of nanofibers, nanosensors, and QDs in neurology is discussed in the preceding sections, with a focus on drug delivery, neuroimaging, and neurodegenerative diseases. However, the specific relevance of QDs, nanofibers, and nanosensors in the detection and treatment of CNS illnesses are discussed in the sections that follow (Table 2).

Template synthesis, drawing, vapor grown, self-assembly [36, 37], electrohydrodynamic direct writing, centrifugal jet spinning, CO₂ laser supersonic drawing [38], plasma-induced synthesis, electrospinning [39], and phase separation [40, 41] are some of the ways for fabricating nanofibers. Nanosensors are cutting-edge, microscopic devices that can be used in molecular engineering and nanomedicine. Sensors are devices that can track changes in analytes and transform them into human-readable signals for vital activities in living systems. However, not all sensors can detect changes in chemical concentration alone; some can also detect changes in electrical signals, such as the action potential of a neuron. In biosensors, however, a biological recognition molecule interacts with the target substance, and response signals are monitored electrically, optically,

Fig. 4 **A** Bright-light-guided and **B** fluorescence-guided surgical resection of glioma in the QDs-c(RGDyK)NP + UTMD and QDs-c(RGDyK) NP – UTMD groups, respectively [29]. Reproduced with permission

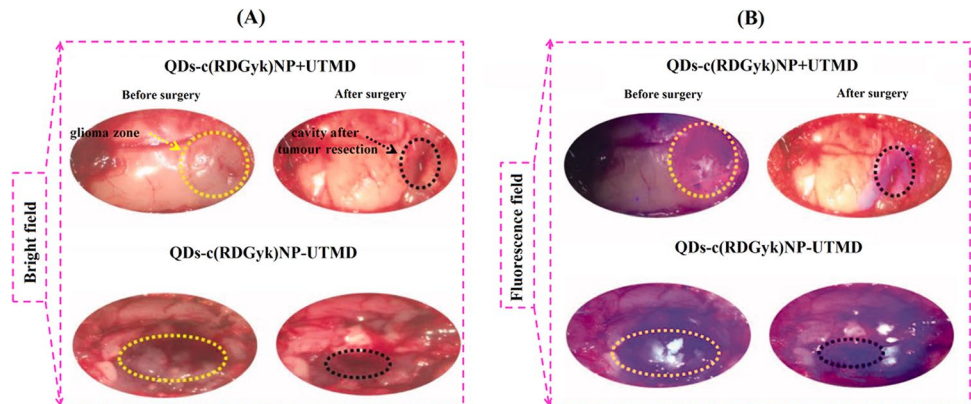


Table 2 Materials for the production of nanofibers and their applications

Polymer type	Examples	Applications	Ref
Natural	Keratin Cellulose	Biomedical engineering Tissue engineering	[30, 31]
Synthetic	Poly l lactic co glycolide (PLGA) Cellulose acetate	Tissue engineering	[32, 33]
Conducting	PANI	Electrodes for dopamine determination	[34]
Composite materials	CNF/carbon black/polyethylene PVP/Au	Microelectrode for neural interface Scaffolds for axons	[35]

and mechanically to determine the concentration of analytes [42, 43]. Nanosensors are often made in one of three ways: bottom-up, top-down, or self-assembly. In electrochemical nanosensors, nanomaterials such as nanowires, nanoribbons, nanotowers, nanorods, and nanotubes are employed as sensing materials [44]. Sensors made employing nanosphere functionalized SiO₂ that act on the surface plasmon resonance (SPR) effect, for example, detect -amino-butyric acid (GABA), which is important in diagnosing brain disorders. The refractive index is used to calculate the concentration of GABA, which is then converted to an optical signal [45, 46]. Increased glucose levels in particular cells can be used to diagnose cancer as it spreads throughout the body. The customized glucose sensors are made by immobilizing the glucose oxidase (GOx) enzyme on the nanopipettes using poly l lysine (PLL) and glutaraldehyde. The sensor can measure glucose levels in fibroblast and cancerous cell lines, and it can be used as a mechanistic tool to discriminate between malignant and non-malignant cells. Such sensors are useful for monitoring the course of cancer in the body in real-time [47].

3 Applications of nanostructures in neuroscience

The usage of nanomaterials can be used to diagnose and treat a variety of neurological illnesses. The size, surface area to volume ratio, biocompatibility, and localized cytotoxicity of nanoparticles have piqued the interest of researchers. Table 3 summarizes various nanomaterials for diagnosing and treating brain damage, Alzheimer's disease (AD), and tumors.

AD is a neuropathological condition characterized by plaques formed by the aggregation of amyloid beta (A) peptides. Small amounts of hazardous compounds are frequently eliminated from the body during normal functioning; however, in AD, an abnormal aging process occurs due to plaque formation. Selenium quantum dots (SeQDs) were created to improve the therapeutic efficacy of medications via the BBB [56]. SeQDS exhibits assertive ROS behavior, inhibits aggregation, and reduces related toxicity. Because of their small size, they pass through the BBB more quickly, and their accumulation in the brain helps to reduce Alzheimer's

disease and improve patients' learning and memory abilities (Fig. 5a). Plaques are metal sinks that reduce the zinc ion levels in the surrounding environment, resulting in lower synapse density. As a result, it can cause cell death and neuroinflammation [49]. Thus, zinc-loaded nanoparticles were utilized to treat Alzheimer's disease in the hopes that high amounts of zinc could reverse the degenerative changes (Fig. 5b). Chemotherapy is the standard treatment for malignant glioblastoma (GB), although it has a number of drawbacks, including systemic toxicity and greater drug concentrations in the tumor site, owing to the BBB. The constraint can be solved by using drug delivery devices to carry medications to the tumor location. Sustained release of DTIC containing polymeric NFs, for example, enhanced its absorption by GB and, as a result, cell death by apoptosis (Fig. 6a) [58]. Similarly, a decrease in cell viability was found when DOX was transported by RGD-coupled graphene QDs, and QDs are beneficial in fluorescent imaging and drug delivery monitoring also [52] (Fig. 6b). Similarly, CTX-modified nanorods transported doxorubicin (Dox) to brain tumors via blood circulation, resulting in considerable suppression of tumor growth [17] (Fig. 6c).

3.1 Nerve regeneration

Despite significant advances in treating neurological illnesses, functional recovery following peripheral nerve injury treatment is still insufficient. Peripheral nerve or axon injuries result in loss of motor or sensory function, and treating these injuries is brutal. Loss of nerve tissue can make axon regeneration difficult, impairing the functioning of the living system. Glaucoma, for example, is a condition in which excessive pressure is inside the eyes, resulting in the degeneration of retinal ganglion cells (RGCs) and axons. This condition has the potential to cause permanent eyesight loss. It is treated by removing the excessive pressure inside the eye without restoring eyesight. Electric simulation (ES) is a new medical technique that can be used to treat neurological problems. The PPy-G hybrid electrospun on ITO substrates utilizing biocompatible poly (lactic co glycolic acid) PLGA and PPy-G/PLGA aligned nanofiber serves as a simulated electrode for RGC regrowth. RGCs' improved cell

Table 3 Nanomaterials for neurological disorder diagnosis and treatment

Applications	Nanomaterials	Methods	Properties	Ref	
NPs	Au NPs Modified with brain brain-targeted exosomes	Serial extrusion method	Au NPs 48 ± 1.5 nm Au NP/exosome 105 ± 10.1 nm	PDI 0.247 ± 0.05 0.430 ± 0.06 PDI 0.08 ± 0.04 0.15 ± 0.05	[48] [49]
	Zinc ions in the vicinity of amyloid aggregates to decrease the probability of Alzheimer disease (AD)	Sonication	g7-NPs 203 ± 14 nm g7-NPs-Zn 220 ± 15 nm	Coated and uncoated nanoparticles are nontoxic	[50]
	Delivery of therapeutic agents across the blood–brain barrier (BBB)	Carboxymethyl cellulose (CMC) coated magnetic nanoparticles (Fe ₃ O ₄ @CMC) containing dopamine hydrochloride	Fe ₃ O ₄ 19.90 ± 3.06 (nm) Fe ₃ O ₄ @CMC 14.05 ± 1.70 (nm)		
	Efficient penetration of chemotherapeutic and diagnostic agents	Peptide-modified gold nanoparticle containing Dox and Gd ³⁺	TAT-Au NPs 5.0 (nm)	Drug Dox is pH sensitive and releases in acidic conditions	[51]
Quantum dots (QDs)	Targeted cancer fluorescence imaging and delivery of anti-tumor drug	Arginine-glycine-aspartic acid (RGD)-conjugated doxorubicin (Dox) containing graphene quantum dots (GQDs)	GQDs (nontoxic) RGD-GQDs-Dox (nontoxic)		[52]
	Near-infrared (NIR) fluorescent imaging for non-invasive visualization and evaluation of the thrombi formation in cerebral blood vessels and pathological state	1100 nm emission peak of lead sulfide (PbS) QDs coated with mercaptoundecanoic acid	PbS QDs (hydrophobic) Mercaptoundecanoic acid modified PbS QDs (hydrophilic)	QDs diameter = < 10 nm	[53]
	Alzheimer’s disease treatment by reducing formation of toxic Aβ-aggregates, maintaining intracellular ROS level, and decreasing abnormal phosphorylation of Tau protein	Selenium quantum dots (SeQDs)	Nano Se 170 nm SeQDs (5 nm)	UV peak-strong absorption peak 310 nm	[54]
	Ratiometric spectral discrimination between cancerous versus healthy cells	Nitrogen (N)-doped; Sulfur (S)-doped; and boron nitrogen (BN) co-doped graphene quantum dots (GQDs)	N-GQDs S-GQDs BN GQDs (3–5 nm)	Appropriate size to cross BBB and biodegrades with time	[55]

Table 3 (continued)

Applications	Nanomaterials	Methods	Properties	Ref	
Nanofiber (NFs)	Cell transplantation to control the neurodegenerative diseases, tissue engineering	Poly(amine) PANI-poly(ϵ -caprolactone) (PCL) blended fibers	Electrospinning	Diameter < 350 nm	Electro conductivity 7.7×10^{-2} S/cm higher than biological fluids biocompatible with neuro stem cells [56]
	Alleviating brain ischemia	Vascular endothelial growth factor (VEGF) loaded poly(ϵ -caprolactone) (PCL) modified nanofiber (NF) membrane	Layer-by-layer (LbL) assembly	PCL VEGF-5 L VEGF-10 L VEGF-15 L VEGF-20 L (hydrophobic)	Controlled release of VEGF-A by NF membrane and inhibition of oxidative stress [57]
	Treatment of malignant glioblastoma (GB)	PVA hydrogels containing dactarbazine (DTIC) nanofibers (NFs)	Electrospinning	Diameter of NFs 275.3 ± 96.2 nm (nontoxic) DTIC loading- $83.9 \pm 6.5\%$ Cytotoxic	Sustained release of DTIC from DTIC loaded NFs over 3 days, drug delivery system for GB [58]
	Drug delivery for neuroprotective dressing	Nanofibrous mat of poly(D,L-lactide-co-glycolide) PDLG polymer containing rhodamine B and bovine serum albumin conjugated with fluorescein (BSA-FITC)	Randomly oriented polymer nanofibers via electrospinning	RB 2.8% (1.97 ± 0.85 nm) BSA-FITC 2% (4.86 ± 0.30)	Porosity (%) 55 40 [59]
Nanorods	Targeted drug delivery for brain tumor treatment	Eu-doped Gd_2O_3 nanorods conjugated with doxorubicin (Dox) and chlorotoxin (CTX)	PEGylation	Eu- Gd_2O_3 NRs (90.9 ± 37) CTX-NRs-Dox (116.3 ± 52)	Dox is pH responsive and releases in acidic conditions [17]

Fig. 5 **a** Detection of decrease in aggregation of A β on application of SeQDs in SH-SY5Y cells [54]. **b** Reduction in mean areas of plaque in cortex of mouse at three optic fields treated with zinc-loaded nanoparticles detected by zinc-staining [51]. Reproduced with permission

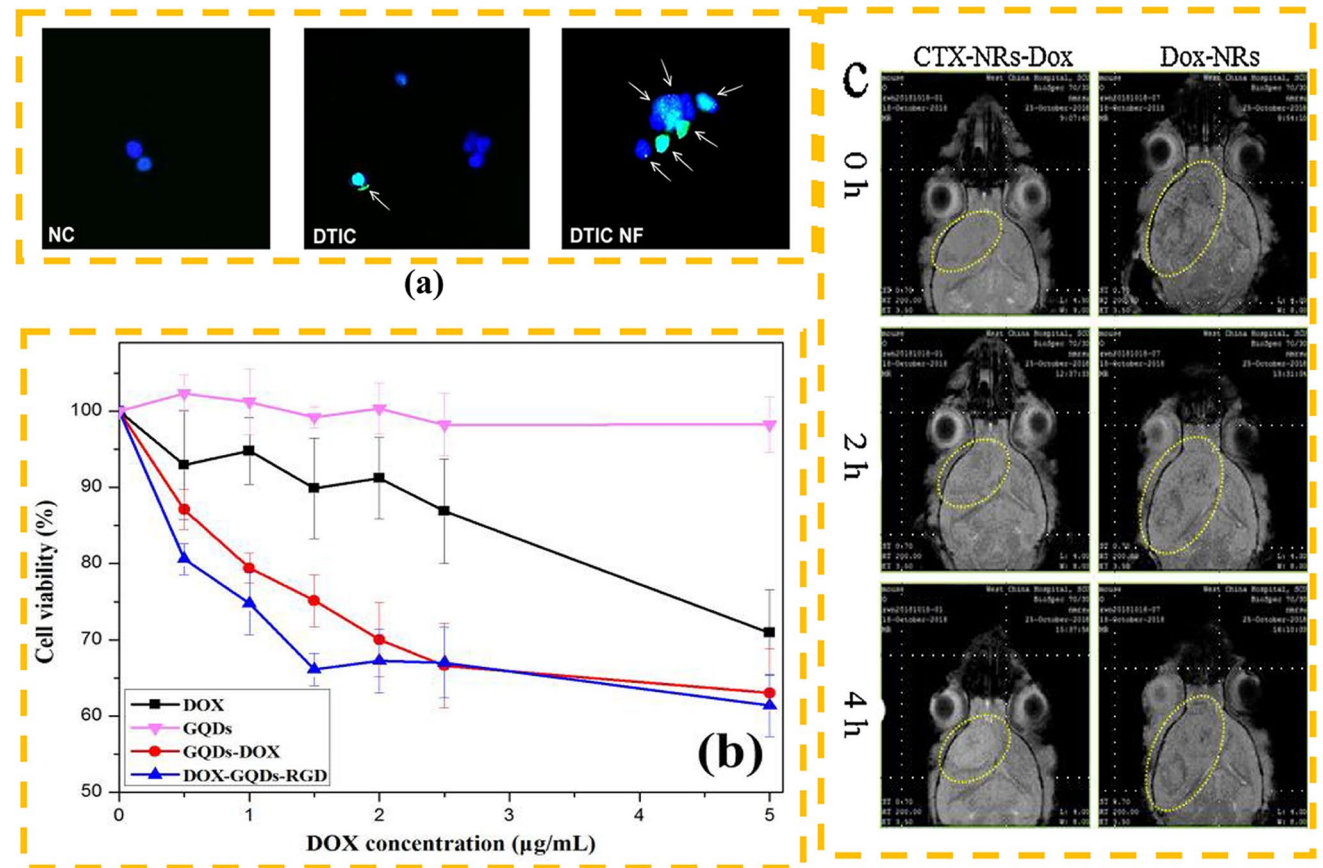
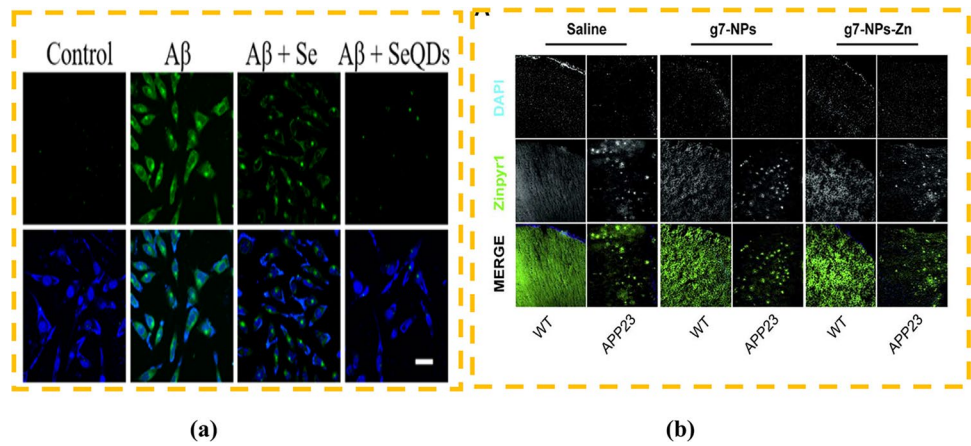


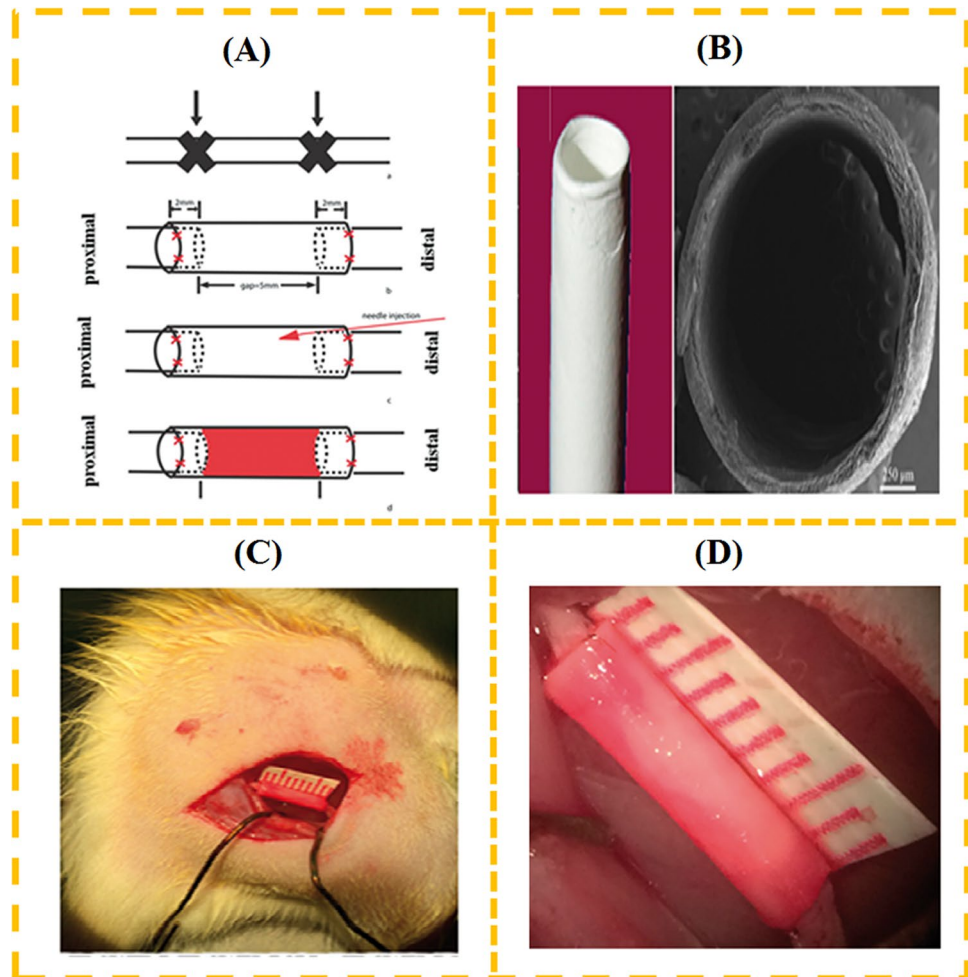
Fig. 6 **a** DNA damage and cell death were assessed using fluorescent pictures after exposure to DTIC, DTIC NF, and no treatment (NC) [58]. **b** Cell viability tests of GQDs, free DOX, GQDs-DOX, and DOX-GQDs-RGD at various DOX doses [52]. **c** MR image of brain

tissue of OTNM mice with transplanted orthotopic glioma acquired 0 h (pre-injection), 2 h, and 4 h after injection of CTX-NRs-Dox and Dox-NRs, respectively, and yellow rings depict tumor field size in the above pictures [17]. Reproduced with permission

survival, cell density, neurite development, and anti-aging capabilities make ES a promising option for primary therapy for the optical nerve [60]. RADA 16-I is a self-assembled peptide (SAP) but has a low pH. RADA 16-RGD and RADA 16-IKVAV were blended to create RADA 16-Mix nanofiber hydrogel at neutral pH to solve

this. The RADA 16-Mix nanofiber hydrogel promoted axonal regeneration from the proximal to the distal position, which was attributed to increased cell movement (Fig. 7). This neuronal synthesis, which has improved functional recovery, could be a candidate for peripheral neural repair [61, 62]. Similarly, PLGA coelectrospun

Fig. 7 Axonal regeneration in the rat was studied using the following methods: **A** injury model and repair strategy, **B** PLLA nanofibrous conduit, **C** rat surgery, and **D** graft transplantation to bridge the nerve gap. [61] Reproduced with permission



Peptide RADARADARADAGGPFSSSTKT (RADA16-I-BMHP1) nanofibers can significantly boost Schwann cell proliferation, infiltration, and gene expression in the therapy of peripheral nerve injury [63]. Aside from these SAPs, electrically conductive 3-D nanofibers (e-NFs) are another emerging material since these innovative materials allow tissue formation by electric stimulation. The electro-responsive nature and physical likeness of nanofiber with neurites of neurons, as well as its flexibility and cell adhesion, are appealing qualities for e-NFs. Because of their fragility, biodegradability, and often-weak electrical charges, standard conducting materials such as polypyrrole (PPy), polyaniline, and carbon nanotubes, as well as their application as e-NFs, are unfavorable. Electrospun nanofibers of poly (vinyl chloride) covered with graphene used to create 3D graphene structures outperform their 2D counterparts. In response to cellular electrical modeling, the extraordinary enhanced proliferation of primary motor neurons validated these tiny structures' tremendous potential for neuroscience [64].

3.2 Microelectrode probes

Understanding and detecting substances in the CNS is an ongoing need better to understand neural signaling, brain functions, and disorders. Edgar Adrian pioneered electrical recordings to research brain activities in the 1930s, and the underlying phenomena have been used to develop such techniques ever since. Microelectrodes are used to explore brain functions outside and have been shown to be helpful in brain-machine interfaces. Metal-based microwires and silicon-based channels are commonly utilized for this purpose. Still, their incompatibility with brain cells in terms of biocompatibility and mechanical strength has caused their use to be discontinued. As a result of in vivo small footprints, there is increased interest in the development of flexible, biocompatible, and resilient microelectrodes. Carbon nanofiber (CNF) composite-based electrodes made by drawing show the improved efficiency in recording multiple neuronal activities next to the electrode compared to CNF-based electrodes. These microelectrodes effectively treat chronic electrophysiological brain research and illness [65].

Glucose levels, in addition to these biochemicals, contribute to the early diagnosis of brain tumors. The PEDOT nanofiber immobilizing glucose oxidase (GOx) enzyme-based nanosensor is sensitive to glucose up to 0.26 mM for +300 mV potential and 0.12 mM for +700 mV potential. A biosensor with this detection limit is appropriate for measuring the glucose level in cerebrospinal fluid based on the biological range of glucose concentrations. Lower polarization potentials are preferable since they extend the biosensor’s lifetime while reducing sensitivity degradation. Physiological systems should be monitored with similar enzyme-specific sensors [66]. Among nanosensors, optode-based nanosensors (OBNs) have gained special attention due to their ability to monitor spatiotemporal ion dynamics during signaling. Intracellular sodium flux was investigated using OBNs as a sensing platform using transparent microelectrodes (TME) made of gold/poly(3,4-ethylenedioxythiophene)-poly-(styrenesulfonate) (Au/PEDOT:PSS) (Fig. 8). TME is more confined and delivers more exact current simulation than field simulation; hence, it provides more control over simulation and a reliable method for ratiometric imaging of Na⁺ flux employing OBNs in dorsal root ganglion (DRG) neurons [67].

3.3 Drug delivery

The efficient treatment of CNS illnesses necessitates targeted medication delivery and the prolonged release of biochemicals from nanocarriers. Parkinson’s disease is a neurodegenerative ailment for which an electrospun film made of Zein nanofibers promotes drug sustained release and boosts drug bioavailability by keeping patients’ blood plasma steady [68]. Aside from controlled release, the topology of nanofibers contributes to neural differentiation by creating a niche for neural differentiation in artificial stem cells. The

electrospun nanofibrous scaffold made of ϵ -caprolactone and ethyl ethylene phosphate copolymer supports the retinoic acid (RA) and neurotrophic factor (BDNF), whereas prolonged release of RA and BDNF from the scaffold enhances and promotes nerve regeneration afterward. Natural extracts have various medical properties that can help with nerve healing. Lycium barbarum polysaccharide (LBP) electrospun in core-shell nanofibrous scaffolds displayed slow release. LBP-containing scaffolds promote PC 12 cell proliferation and neural development [69]. However, due to quick clearance from bodies, direct administration of medications may not always generate the desired results, increasing the requirement for biodegradable scaffolds. Although self-assembled peptide nanofiber-based scaffolds are used, they cannot support axon regeneration via extensively disordered damaged tissues. As a result, a poly(ϵ -caprolactone-co-ethyl ethylene phosphate) (PCLEEP) nanofibers-based electrospun scaffold distributed in a collagen hydrogel encapsulating the model protein neurotrophin-3 (NT-3) and microRNA can be used [70]. Protein promotes axonal sprouting, whereas RNA helps axons produce protein. These scaffolds, which provide regulated medication administration while supporting brain regeneration with little visible inflammation, are promising tissue engineering materials (Fig. 9). The development of gold-silica rattle revealed the tremendous therapeutic and imaging potential of quantum sized gold nanoparticles (NPs). The hydrophobic gold surface has a considerable surface area, which increases the drug-carrying potential of the drug doxorubicin (DOX) while also extending its release. Although Au NPs tend to clump together and bind to proteins, resulting in cytotoxicity and decreased efficiency, this was mitigated by using hollow silica. QRs can be employed as a contrasting agent for MRI imaging because of their paramagnetic nature. In addition, QRs-treated tumor cells killed more cells during photothermal treatment (PTT),

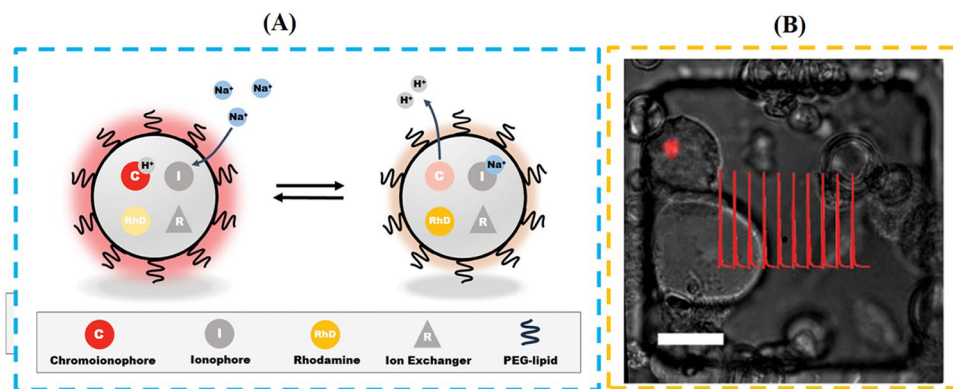


Fig. 8 **A** The mechanism of action of optode-based nanosensors (OBNs) for selective recruitment of sodium ion to the sensor results in deprotonation of two fluorophores, C and RhD, to maintain charge neutrality. This results in a change in the ratiometric fluorescence

intensity in the signal readout. **B** OBNs (red) are first microinjected into the DRG using one of the two 4 stimulation clear microelectrodes (TME) (Reproduced with the permission [67] copyright, 2018. American Chemical Society)

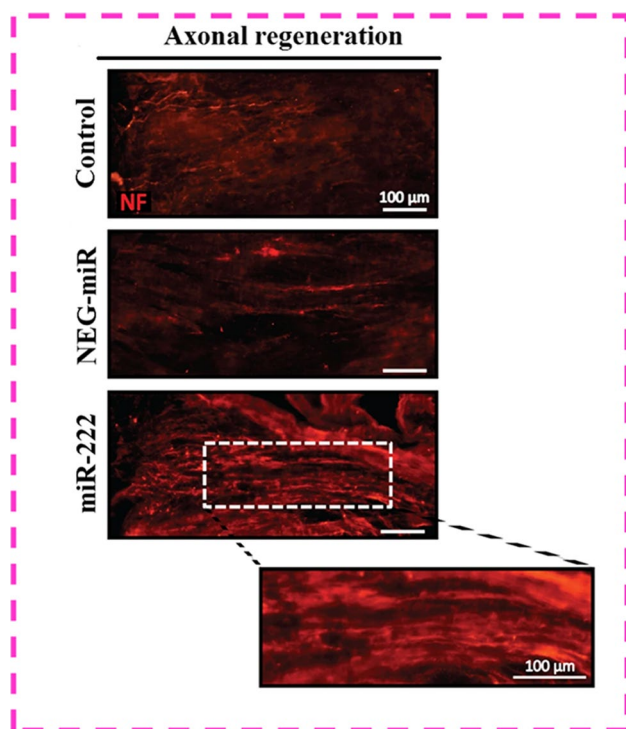


Fig. 9 At 10 days post-implantation increased, axonal regeneration within nanofiber-hydrogel scaffolds. Reproduced with permission [70]

and the needed dose mg kg^{-1} is lower than Au NPs and mesoporous silica [71].

3.4 Detecting chemicals/biomolecules

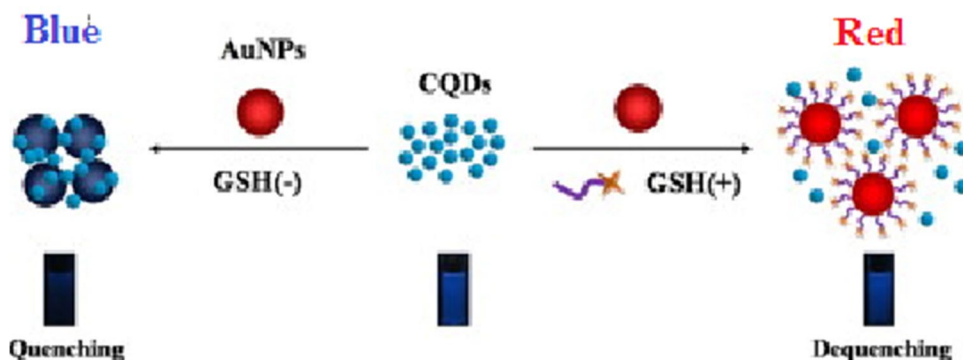
Nanosensors are promising tools for monitoring changes in neurotransmitter, ion, and cancer biomarker concentrations and detecting neurotransmitters such as acetylcholine, which are made utilizing acetylcholine-catalyzing enzymes in conjunction with gadolinium. When acetylcholine is hydrolyzed with enzyme, the pH changes, indicating the presence of acetylcholine. Although Na^+ ions play a vital function in altering the electrochemical gradient in intracellular

signaling and carrying a charge for synaptic currents, the production of Na^+ ion monitoring instruments is slow. These nanosensors establish the groundwork for developing sensing agents to help researchers better comprehend the brain's other neurotransmitters [72, 73]. Glutathione (GSH) is a peptide that functions in various biological processes, including the control of intracellular signaling and redox activities. All primary bodily fluids, including cerebrospinal fluid, contain it. Its concentration is minimal, but if it surpasses the threshold, it can cause cancer, liver damage, and psoriasis, among other things. GSH is difficult to detect because it has a thiol group comparable to other biothiols (cystein). Nanosensors made of Au NPs and QDs that work on colorimetric and fluorescence phenomena may detect GSH at concentrations as low as 50 nM with high precision (Fig. 10). Because of the increased inter particle distance and protection of the Au NPs from aggregation, the GSH interaction with Au NPs changes color from blue to red [74]. Intercellular and intracellular information is transmitted via neurotransmitters. In contrast to electrical potential, chemical signals require great spatial and temporal precision to be measured. Surface immobilized nanosensors based on DNA/SWCNTs incorporating PC 12 cells can detect the presence of dopamine in the near-infrared. The nanosensors enabled a far higher resolution measurement of spatial and temporal dynamics of dopamine release after stimulation with potassium buffer solution than was previously possible [75]. Similarly, fluorescent sensors with core/shell hybrids made of polypropylene (PPy) and graphene quantum dots (GQDs) exhibited high sensitivity for DA. Compared to pure GQDs and semiconductor QDs, these sensors have a higher detection limit [76].

4 Conclusions and future perspective

Nanotechnology has impacted many industries, including electronics, water treatment, industrial production, measuring devices, packaging, textiles, and healthcare. Nanotechnology's utility in these and other domains is not limited

Fig. 10 The schematic diagram of the principle of of GSH detection through the dual-mode nanosensor with both colorimetric and fluorometric readout. Reproduced with permission [74]



to NPs, thin films, CNTs, and graphene but is continually growing. The roles of nanostructures (NPs, nanocarriers, nanotubes, dendrimers, QDs, and micelles) in diagnosing, imaging, and therapy of neuro diseases were discussed in this review paper. We use real-world examples to demonstrate how nanostructures can help overcome the shortcomings of the BBB in drug delivery and imaging. In addition, a brief overview of nanofibers, nanosensors, and quantum dots interacting with the nervous system is provided, focusing on drug administration, chemical/biochemical release, microelectrode probing, and nerve regeneration. Nanofibers are used to construct nanosensors or as scaffolds. In addition to focused drug delivery, nanofibers can help with neuronal differentiation and regeneration. Nanosensors, on the other hand, can measure the release of neurotransmitters and other substances such as glucose and glutathione when nanostructures are exploited and innovated. QDs have size-tunable emission spectra, and they may be conjugated with various biological molecules, making them helpful in imaging, drug administration, and as probes in sensor design. These examples demonstrate how combining nanotechnology and neurology has enabled us to identify molecular-level issues through targeted (site-specific) medication administration, bioimaging, and guided surgery. However, to make putative nanotherapeutics commercially available, thorough toxicokinetic studies are required. The medical community is becoming more aware of the effectiveness and promise of nanofibers, nanosensors, and QDs. The rationale is their ease of processing, tunability, cost-effectiveness, and equivalent results to present technologies. However, while these nanomaterials show considerable promise in lab trials, they cannot be scaled up without extensive surface alterations to impart the needed sensitivity. Ultimately, this can impair the detection limit and reproducibility of results in pilot scale research. Such constraints can be mitigated by creating alternative nanomaterial creation and modification approaches. Furthermore, questions about the performance and reaction of nanomaterials (in vivo) remain unanswered. Moreover, toxicity, which typically rises at the nanoscale due to the enormous surface area, is poorly understood and necessitates extra attention and emphasis when designing nanofibers and nanosensors for neural interfaces. Thus, after developing tight safety measures for production, dosage, and application, the availability of these efficacious and safe medicines to neuropractitioners is anticipated in the near future.

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