Coordination Chemistry Reviews 501 (2024) 215519

Contents lists available at ScienceDirect

Coordination Chemistry Reviews

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

Review

Nanozyme-based strategies for efficient theranostics of brain diseases

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ARTICLE INFO

Keywords:
Nanozymes
ROS regulation
Brain diseases
Diagnostics
Therapeutics
Antioxidant

ABSTRACT

Oxidative stress emerges as a critical mechanism underlying the development and progression of various brain diseases, arising from either increased generation of reactive oxygen species (ROS) or dysfunction of the antioxidant defense system. Nanozymes, possessing enzymatic catalytic capabilities alongside the physicochemical characteristics of nanosized materials, have showcased extraordinary promise in regulating the production or scavenging of ROS. Consequently, nanozymes have been utilized to detect the basic level and dynamic changes of neurochemical biomarkers closely related to physiological and pathological brain conditions, as well as to mitigate oxidative damage and facilitate the penetration of the blood-brain barrier. As such, nanozymes have emerged as a promising tool for developing diagnostic and therapeutic approaches for various neurological disorders. This review offers a comprehensive overview of the catalytic mechanisms exhibited by nanozymes, which have demonstrated tremendous potential in the effective diagnosis and treatment of brain disorders. Through summarizing the emerging methods for applying nanozymes, this review aims to provide directions on the rational design of nanozymes for the theranostics of brain diseases. Additionally, this review seeks to address the current challenges and delineate future directions for the advancement of this field.

Abbreviations: Ach, acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's Disease; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; AUR, Amplex UltraRed; Aβ, amyloid β protein; BBB, blood-brain barrier; Bor, borneol; BSA, bovine serum albumin; CAs, carbonic anhydrases; CAT, catalase; CD, carbon dot; CDT, chemodynamic therapy; Ce, ceria; Ch, choline; ChOx, choline oxidase; CM, cerebral malaria; CPD, cyclobutane pyrimidine dimers; Cys, cysteine; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; ECM, experimental cerebral malaria; ECs, endothelial cells; Eda, edaravone; FAD, flavin adenine dinucleotide; GBM, glioblastoma multiforme; GDH, glucose dehydrogenase; GOx, glucose oxidase; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; H_2O_2, hydrogen peroxide; HD, Huntington's Disease; HDAC, histone deacetylase; HFn, human H-ferritin; HRP, horseradish peroxidase; HTT, huntingtin; IS, ischemic stroke; K_M, Michaelis-Menten constant; k_{cat}, catalytic constant; k_{cat}/K_M, specificity constant; LOx, lactate oxidase; MOF, metal-organic framework; MSN, mesoporous silica nanoparticles; MRI, magnetic resonance imaging; NAs, nano-alloys; NAD (P), nicotinamide adenine dinucleotide (phosphate); NCs, nanoparticle clusters; NLRP3, NLR family pyrin domain containing 3; NPs, nanoparticles; $O_2^{\bullet-}$, superoxide anion radical; $^1O_2$, singlet oxygen; OH^-, hydroxide ions; $ONOO^-$, peroxynitrite; OPH, organo-phosphorus hydrolase; OXD, oxidase; PD, Parkinson's Disease; PDT, photodynamic therapy; PDNPs, polydopamine nanoparticles; POD, peroxidase; POM, polyoxometalate; POMD, POM with Wells-Dawson structure; PPO, polyphenol oxidase; PQQ, pyrroloquinoline quinone; PTT, photothermal therapy; RBCs, red blood cells; rGO, reduced graphene oxide; RNS, reactive nitrogen species; RONS, reactive oxygen and nitrogen species; ROS, reactive oxygen species; Se, selenium; Sec, selenocysteine; SERS, surface-enhanced Raman scattering; SNc, Substantia Nigra compact; SOD, superoxide dismutase; TBH, *tert*-butyl hydroperoxide solution; TBI, traumatic brain injury; Tf, transferrin; TMB, 3,3′,5,5′-tetramethylbenzidine; TME, tumor microenvironment; TPH2, tryptophan hydroxylase-2; TPx, thiol peroxidase; ZIF, zeolitic imidazolate framework; UV, ultraviolet; V_{max}, maximum reaction rate; $^{\bullet}NO$, nitric oxide; $^{\bullet}OH$, hydroxyl radical; 3,5-DTBC, 3,5-3,5-*Di-tert*-butylcatechol; 4-HNE, 4-hydroxynonenal; α-syn, α-synuclein.

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https://doi.org/10.1016/j.ccr.2023.215519
Received 9 August 2023; Accepted 16 October 2023
Available online 1 December 2023

1. Introduction

Brain diseases, as a broad term, are used to describe a range of nervous system diseases affecting the structural and functional integrity of the brain,[1] including ischemic stroke (IS),[2] traumatic brain injury (TBI),[3] tumor,[4] and neurodegenerative disease.[5–7] Structurally, the brain is protected by the blood-brain barrier (BBB), which selectively prevents the ingress of deleterious substances, while resulting in low permeability of drugs. It is the Achilles Heel for the poor theranostics of brain diseases.[8,9] Functionally, the brain belongs to the central nervous system, responsible for consciousness and behavior.[10,11] The brain diseases are often accompanied by serious consciousness and behavior disorders. With the continuous growth and aging of the global population, the burden placed upon public healthcare by neurological disorders has increased significantly.[12,13] More importantly, brain diseases affect patients' quality of life seriously.[14,15] So new methods, strategies and technologies are called for the theranostics of brain diseases.

Redox assumes a paramount significance in the initiation and progression of brain diseases.[16] For example, ROS storm generated by reperfusion is the main cause of poor prognosis in IS.[17] Degenerative diseases and depression are always accompanied by increased oxidative stress.[5,18] Oxidative stress is increasingly used as an indicator for brain diseases treatment and prognosis evaluation. The clear core definition of nanozymes is "nanomaterials that catalyze the conversion of enzyme substrates to products and follow enzymatic kinetics (*e.g.* Michaelis-Menten) under physiologically relevant conditions".[19] However, given that nanozymes can also work under harsh conditions, the boundaries of the definition of nanozymes are fuzzy and will be updated as the field rapidly develops. Since first reported in 2007,[20] nanozymes have attracted considerable attention in redox regulation on account of obvious advantages over natural enzymes, including ease of synthesis in large quantities, cost-effectiveness, exceptional stability, versatile and tunable catalytic capabilities (Table 1).[21,22] Moreover, growing works have reported that nanozymes have the potential to penetrate the BBB by various pathways such as endocytosis and transcytosis.[23,24] Some nanozymes like nanozyme coated by ferritin have unique ability to effectively penetrate the BBB based on the transcytosis mediated by transferrin receptor 1.[25] Additionally, nanozymes can be easily modified by active substances,[26] peptides[27] and receptors [28] to improve their performance in penetrating the BBB. Given these advantages, nanozymes have been designed to effectively treat brain diseases and monitor the basic level and changes of neurochemical biomarkers related to brain physiological and pathological conditions, which confirms the feasibility of nanozymes to intervene in pathological processes.[29–31]

So far, several scholarly reviews have been published on the utilization of nanozymes in neurological disorders, covering IS, TBI and neurodegenerative diseases. However, the systematic consolidation of information concerning other important neurological diseases, such as brain cancer, cerebral malaria (CM), and depression, remains lacking. In this review article, we comprehensively summarize the catalytic mechanisms of nanozymes, systematically review their pre-clinical applications across diverse brain diseases (Fig. 1), and discuss the challenges in practical applications. We hope to provide a platform for sparking interests among researchers interested in nanozymes and promoting nanozymes to better serve for human health.

Table 1
Advantages and challenges of nanozymes compared with natural enzymes.

Advantages [21,22]	Challenges[32]
• simpler preparation process	• catalytic activity and selectivity of most nanozymes are expected to improve
• lower preparation cost	• researches on more kinds of enzyme-like activities and nanozymes with multienzyme-like activities are needed
• higher stability	• more energy to explore catalytic kinetics and mechanism of nanozymes needs to be devoted
• more functions in theranostics of diseases	• more applicable scenarios should be developed
• better controllability due to the easy modification	• biosafety and potential toxicity still remain challenging

2. The enzyme-like activities and mechanisms of nanozymes

The natural enzymes encompass seven distinct classifications, which are oxidoreductases, transferases, hydrolases, lyases, isomerases, ligases, and translocases, responsible for biological reactions in living systems.[33] Among these, oxidoreductases-like, hydrolases-like, lyases-like and isomerases-like nanozymes have been developed (Table 2) (Fig. 2). [34]

Nanozymes typically exhibit a kinetic mechanism consistent with natural enzymes, namely Michaelis-Menten kinetics.[35] As one of the most typical enzyme kinetic equations, the Michaelis-Menten equation (1) represents the quantitative relationship between substrate concentration ([*S*]) and enzyme reaction rate (v), which is used to describe the ability of the enzyme to bind substrates, the catalytic reaction rate and the factors affecting reaction rate. Kinetic constants include the maximum reaction rate (V_{max}), Michaelis-Menten constant (K_M), catalytic constant (k_{cat}) and specificity constant (k_{cat}/K_M).[36]

$$v = \frac{V_{max}[S]}{K_m + [S]} \quad (1)$$

Based on the catalytic mechanisms of natural enzymes, this section will focus on reviewing the biomimetic catalytic mechanisms of various nanozymes. Given the multi-enzyme activity of some nanozymes, the mechanisms with multi-step/series reactions are also described, which can synergistically act on multiple substrates or be regulated by different environments to achieve specific catalysis.

2.1. Oxidoreductases

The main type of nanozymes are oxidoreductases, which are also the most studied and applied class. Oxidative stress stands as a negative factor precipitating brain dysfunction. In living organisms, the balance of redox levels is maintained by natural enzymes.[66] However, it may be disrupted under pathological states through the augmentation of ROS and reactive nitrogen species (RNS) or the impairment of antioxidant systems,[67] leading to oxidative stress. Oxidative stress damages biomacromolecules (proteins, lipids, and DNA), and blocks normal signaling pathways.[68,69] Reductases-like nanozymes, such as catalase (CAT), glutathione peroxidase (GPx), and superoxide dismutase (SOD), are considered as potential solutions to the above problems, and are expected to scavenge RONS and mitigate oxidative damage.[21,22,70] In addition, a general application of oxidases (OXD)-like and peroxidase (POD)-like nanozymes has been observed in the treatment of diseases such as wounds and cancers, and construction of multifunctional biosensors that sensitively detect neurochemical biomarkers closely related to brain physiological and pathological conditions.

2.1.1. Oxidase

Oxidation reactions are essential for aerobic metabolism, with ROS such as superoxide anion radical ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), and singlet oxygen ($^1O_2$) as by-products.[71] With O_2, natural OXD can catalyze substrates to the corresponding oxidation products, while O_2 is incorporated into the reaction products or accepts electrons for conversion into H_2O or H_2O_2 (2, 3). OXD is usually named according to the substrates, such as glucose oxidase (GOx), *etc*. At present, extensive experimental evidences have substantiated that nanomaterials exhibit OXD-mimicking activity. For example, Au@Pt mimics ascorbate oxidase-like activity,[43] P-MoO_{3-x} nanoparticles (NPs) mimic sulfite oxidase-like activity,[44] and Fe-N-doped graphene mimics

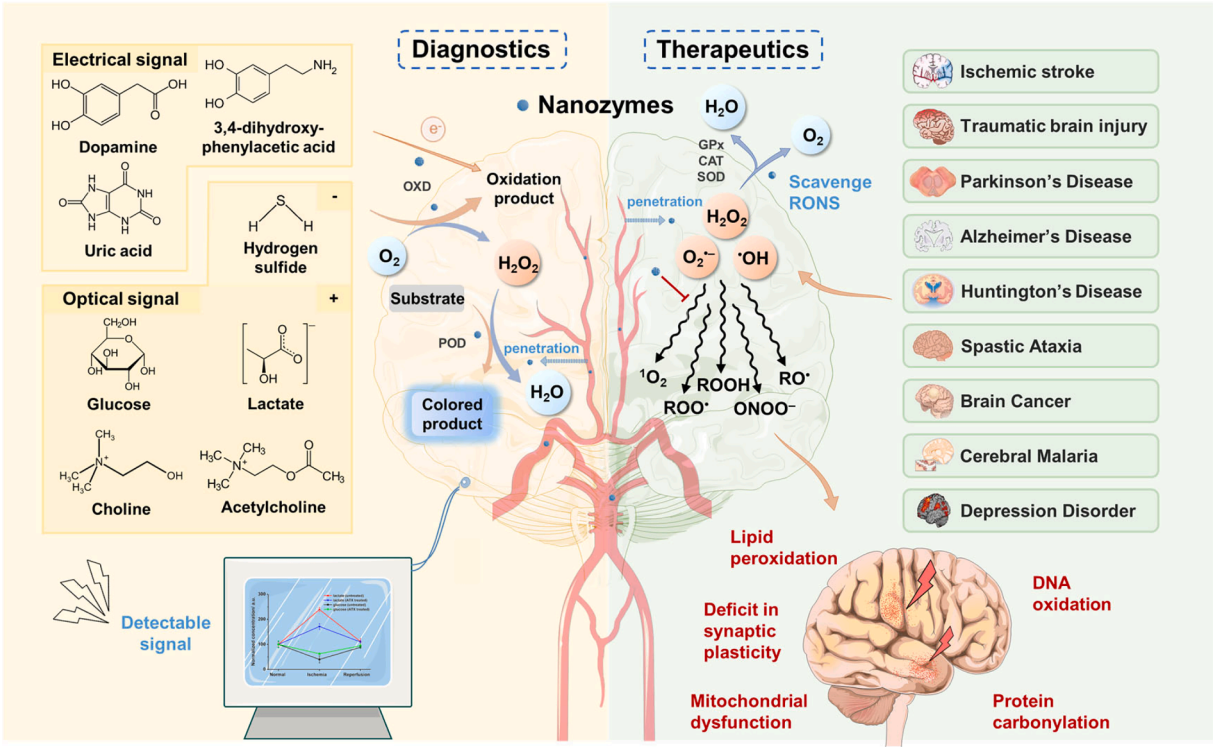

Fig. 1. Overview of nanozymes-based theranostics of brain diseases. Nanozymes engineered for enhanced brain targeting readily traverse the BBB. On the one hand, nanozymes can directly or indirectly catalyze neurochemicals to generate detectable signals, allowing for the monitoring of brain physiological or pathological conditions and the diagnosis of brain diseases. On the other hand, numerous brain diseases are intricately associated with the excessive production of ROS. ROS-mediated oxidative stress and excessive inflammatory responses seriously impair neurological functions. Nanozymes possess the remarkable capacity to modulate the generation or elimination of ROS, thereby realizing the efficacious management of brain diseases. Blood vessels and brain structure diagrams are provided by Servier Medical Art (http://smart.servier.com) under CC BY 3.0 license.

NADPH oxidase-like activity.[45] Most OXD-like nanozymes have lower K_M values than natural enzymes, meaning a high affinity for substrates. But their specificity is relatively low and they can catalyze multiple substrates such as 3,3′,5,5′- tetramethylbenzidine (TMB), glucose, catechol, and *o*-phenylenediamine.[41]

$$4AH + O_2 \rightarrow 4A + 2H_2O \quad (2)$$

$$AH + O_2 + 2H_2O \rightarrow A + 2H_2O_2 \quad (3)$$

Glucose oxidizing enzymes are divided into two types: glucose dehydrogenase (GDH) and GOx. GDH uses nicotinamide adenine dinucleotide (phosphate) (NAD(P)) or pyrroloquinoline quinone (PQQ) as the electron acceptor to oxidize glucose in one step (4).[72] While GOx uses a two-step mechanism, flavin adenine dinucleotide (FAD) cofactor assumes the role of an intermediate electron acceptor to oxidize *β*-d-glucose, leading to the formation of d-glucono-*δ*-lactone. Thereafter, the intermediate $FADH_2$ is oxidized by the terminal electron acceptor O_2 to generate FAD and H_2O_2 (5, 6).[73] Both reaction types are dehydrogenation reactions, that is, primarily functioning as an electron acceptor, the oxidant exerts its influence without engaging in direct reactivity with the substrates.

$$\text{glucose} + 2NAD/2NADP/PQQ \rightarrow \text{gluconolactone} + 2NADH/2NADPH/PQQH_2 \quad (4)$$

$$\text{glucose} + GOx(FAD) \rightarrow \text{gluconolactone} + GOx(FADH_2) \quad (5)$$

$$GOx(FADH_2) + O_2 \rightarrow GOx(FAD) + H_2O_2 \quad (6)$$

In 2004, bare Au NPs were found to have the ability to oxidize glucose, being able to catalyze 21% of glucose into gluconate within 200 s. A series of kinetic experiments characterizing glucose oxidation revealed a linear correlation between catalytic activity and gold concentration (10^{-5}-10^{-6} M).[37] Subsequent studies supported this result and revealed how Au NPs catalyzed the oxidation of glucose. After hydroxide ions (OH^-) as Brønsted base removed the C1 hydroxyl proton of glucose, the formed hydrated glucose anion was adsorbed on Au NPs, and O_2 was reduced to H_2O_2 by nucleophilic attack (Fig. 3**a**).[38] This reaction follows typical Michaelis-Menten kinetics and bears a close resemblance to the reaction pathway of natural GOx. The only difference is that OH^- replaces the His residue of GOx to break the C–H bond.[39] Based on this, Au NPs can be developed as a glucose sensor in combination with POD, or be developed for cancer therapy through depleting glucose in malignant cells.[74]

As a copper-containing enzyme, natural polyphenol oxidase (PPO) exhibits the capacity to facilitate the oxidation of an assortment of phenolic compounds, leading to the formation of highly active *o*-quinones. The oxidation is accomplished in two steps: after the ortho hydrogen of the existing hydroxyl group is hydroxylated, *o*-dihydroxybenzene is oxidized to *o*-benzoquinone (Fig. 3**b**). According to different substrates and mechanisms of action, PPOs are divided into three categories: catechol oxidase, tyrosinase, and laccase.[75]

Li *et al.* constructed MOF-818 with a trinuclear copper center designed to mimic the active site of natural catechol oxidase. Remarkably, the nanozyme exhibited activity in catalyzing catechol oxidation while demonstrating the absence of POD-like activity. In acidic or alkaline environments, MOF-818 specifically promoted the oxidation of Di-*tert*-butylcatechol (3,5-DTBC), but could not catalyze the oxidation of TMB and ABTS. It was found that the catalytic action of the tricopper(II) center resulted in the rapid conversion of 3,5-DTBC into 3,5-di-*tert*-butyl-*o*-benzoquinone (3,5-DTBQ) center, while O_2 was reduced to H_2O_2 in the reoxidation catalytic cycle (Fig. 3**c**). After fixing the MOF-818 concentration, the oxidation kinetics were studied by changing the 3,5-DTBC concentration. Calculated values V_{max} (3.17×10^{-6} M/s), K_M

Table 2
The enzyme-like activities of nanozymes.

Catalytic types	Subclasses		Featured Nanozymes	References
oxidoreductases	oxidase	glucose oxidase	Au NPs	[37–39]
		lactate oxidase	Co_4N/C	[40]
		catechol	MOF-818	[41]
		oxidase	CHzyme (Cu-His)	[42]
		ascorbate oxidase	Au@Pt	[43]
		sulfite oxidase	P-MoO_{3-x} NPs	[44]
		NADPH oxidase	Fe-N-doped graphene	[45]
	peroxidase	peroxidase	AuNPs@CDs	[46]
			Fe_3O_4	[20,47]
		glutathione peroxidase	Se@pDA	[48]
			Au NPs (Sec-Arg-Gly-Asp-Cys)	[49]
	catalase		CeO_2 NPs	[50,51]
	superoxide dismutase		Ag, Pd, Pt, and Au and alloys	[52]
			$Au_{4-x}M_x$ (M = Ag, Pd, Pt)	
			Carbon dot nanozyme	[53]
hydrolases	phosphatase		MOFs	[54]
			Ce-FMA-MOF	[55]
			Zn-heptapeptide bionanozymes	[56]
	glycosidase		Cu_3P	[57]
	esterase		PtNP	[58]
	nuclease		Pt	[59]
lyases	carbonic anhydrase		Amino acid-functionalized fullerene	[60]
			ZIF-8	[61]
	photosynthase		TiO_2	[62]
			CeO_2	[63]
isomerases	topoisomerase I		Carbon dots	[64]
	peroxynitrite isomerase		H-RGO	[65]

(8.10×10^{-4} M), k_{cat} (0.383 s^{-1}) and k_{cat}/K_M (4.73×10^2 $M^{-1}s^{-1}$) indicated that MOF-818 has excellent catechol oxidase-like activity. [41] Li *et al.* devised a strategy to engineer a novel nanozyme (CHzyme) with catechol oxidase-like properties, incorporating copper and histidine as key constituents. Furthermore, they combined the enzyme-catalyzed reaction with Schiff base chemistry to realize a cascade reaction. CHzyme oxidizes catechol to o-quinone, and the carbonyl of o-quinone reacts with the amino group in o-phenylenediamine, forming a fluorescent product. In contrast to the conventional enzyme-linked immunosorbent assay, the detection sensitivity is increased by 15 times.[42] Catecholamines (dopamine (DA), norepinephrine, and epinephrine), as key neurotransmitters, are considered to be important indicators of neuroblastoma, schizophrenia, Parkinson's disease (PD), and other neurological diseases,[76] so the investigation into the PPO-like activity of nanomaterials and elucidation of its distinctive catalytic mechanism hold immense significance.

2.1.2. Peroxidase

The POD family is very huge and commonly exists in various types of cells in eukaryotes. It has multiple isoforms, and the major component is heme peroxidase containing Fe (III) protoporphyrin IX as a prosthetic group. It mainly uses peroxide (H_2O_2/ROOH) as an electron receptor to catalyze oxidation of various substrates (7, 8).[77] Typical substrates include phenols, amines, polycyclic aromatic hydrocarbons, and sulfonates.[78]

$$2AH + H_2O_2 \rightarrow 2A + 2H_2O \quad (7)$$

$$2AH + ROOH \rightarrow 2A + ROH + H_2O \quad (8)$$

In the catalytic cycle, the first step is the interaction of H_2O_2 with the Fe(III) atoms in the heme group to generate the transient intermediate iron hydroperoxide. Subsequently, the distal oxygen of iron hydroperoxide is protonated, promoting the cleavage of the O-O bond, forming compound I containing a Fe(IV) oxoiron base center and a porphyrin radical (9). Then, with the participation of reducing substrate, compound I is converted into compound II, and the porphyrin free radical is eliminated, but iron still exists in the Fe(IV) state (10). Finally, compound II returns to the resting state of the enzyme (11).

$$H_2O_2 + Fe\ (III) \rightarrow Fe\ (III)\text{-}O\text{-}OH + H^+ \rightarrow Fe\ (IV) = O\ (\text{compound I}) + H_2O \quad (9)$$

$$Fe\ (IV) = O\ (\text{compound I}) + SH \rightarrow Fe\ (IV)\text{–}OH\ (\text{compound II}) + S^{\bullet} \quad (10)$$

$$Fe\ (IV)\text{–}OH\ (\text{compound II}) + SH \rightarrow Fe\ (III) + H_2O + S^{\bullet} \quad (11)$$

The POD-like activity of nanomaterials is the earliest confirmed activity, and the types of POD-like nanomaterials have gradually expanded from Fe_3O_4 to other metals, metal oxides, carbon nanozymes, and MOFs. The inorganic nanomaterial-based nanozymes typically provide intrinsic POD-mimicking activity, which catalyze the oxidation of colorless TMB to blue amine or diamine. This reaction can be used as disease diagnosis strategies.[79] For example, AuNPs@CDs designed by Zheng *et al.* facilitated the electrons transfer from TMB to H_2O_2.[46] PtNPs/GO proposed by Zhang *et al.* exhibited POD-like activity and catalyzed the color reaction of TMB in the presence of H_2O_2.[80] In addition, common chromogenic substrates include Amplex UltraRed (AUR), *o*-phenyl-enediamine, and di-azo-amino-benzene. For example, Chang *et al.* developed Au/Ag NPs, which can catalyze the reaction of AUR with H_2O_2 to form fluorescent products, thereby detecting acetylcholine (ACh) and diagnosing neurodegenerative diseases.

One of the most typical nanozymes with POD-like activity is Fe_3O_4 nanozyme. Similar to natural horseradish peroxidase (HRP), there is a ping-pong mechanism and Michaelis–Menten kinetics involved in Fe_3O_4 nanozyme. In terms of the catalytic mechanism, the nanozyme first binds and reacts with the corresponding substrate, and releases the product before reacting with the next substrate. Taking the color reaction of H_2O_2 and TMB catalyzed by Fe_3O_4 nanozyme as an example, the K_M value of substrate TMB catalyzed by Fe_3O_4 is smaller than that of natural HRP, but the K_M value of another substrate H_2O_2 catalyzed by Fe_3O_4 is larger than that of natural HRP. Furthermore, the k_{cat} value of Fe_3O_4 is larger than that of natural HRP due to the large specific surface area and enriched active sites.[20] Previous studies on the catalytic mechanism of Fe_3O_4 or other POD-like nanozymes have led to the conclusion of Fenton or Fenton-like reactions, as well as surface-mediated electron transfer processes.[81] Recently, Dong *et al.* reported that Fe_3O_4 nanozymes possess self-depletion properties due to electron transfer within the internal atoms.[47] The structure and intramolecular charge transfer can greatly affect the catalytic performance of materials,[82] indicating that surface and internal atoms should be considered simultaneously in the design, modulation, and application of nanozymes. More specifically, Zhao *et al.* modulated the Co number near N in the Co_x-N nanocomposite, engineering the electronic properties at the N center to mimic lactate oxidase (LOx).[40] Ji *et al.* controlled the electronic configuration of the monatomic iron active site by the precise coordination of phosphorus and nitrogen to achieve POD-mimicking catalytic activity and kinetics on par with that of natural enzymes.[83] Those researches remind us to pay attention to the geometric structure and electronic coordination between active centers and nonmetals in the process of simulating natural enzymes.

2.1.3. Glutathione peroxidase

GPx isozymes are mainly composed of 8 subfamilies, which fulfill a crucial function in antioxidant defense due to their inherent ability to facilitate the reduction of ROS. Except for GPx5, GPx7, and GPx8, the

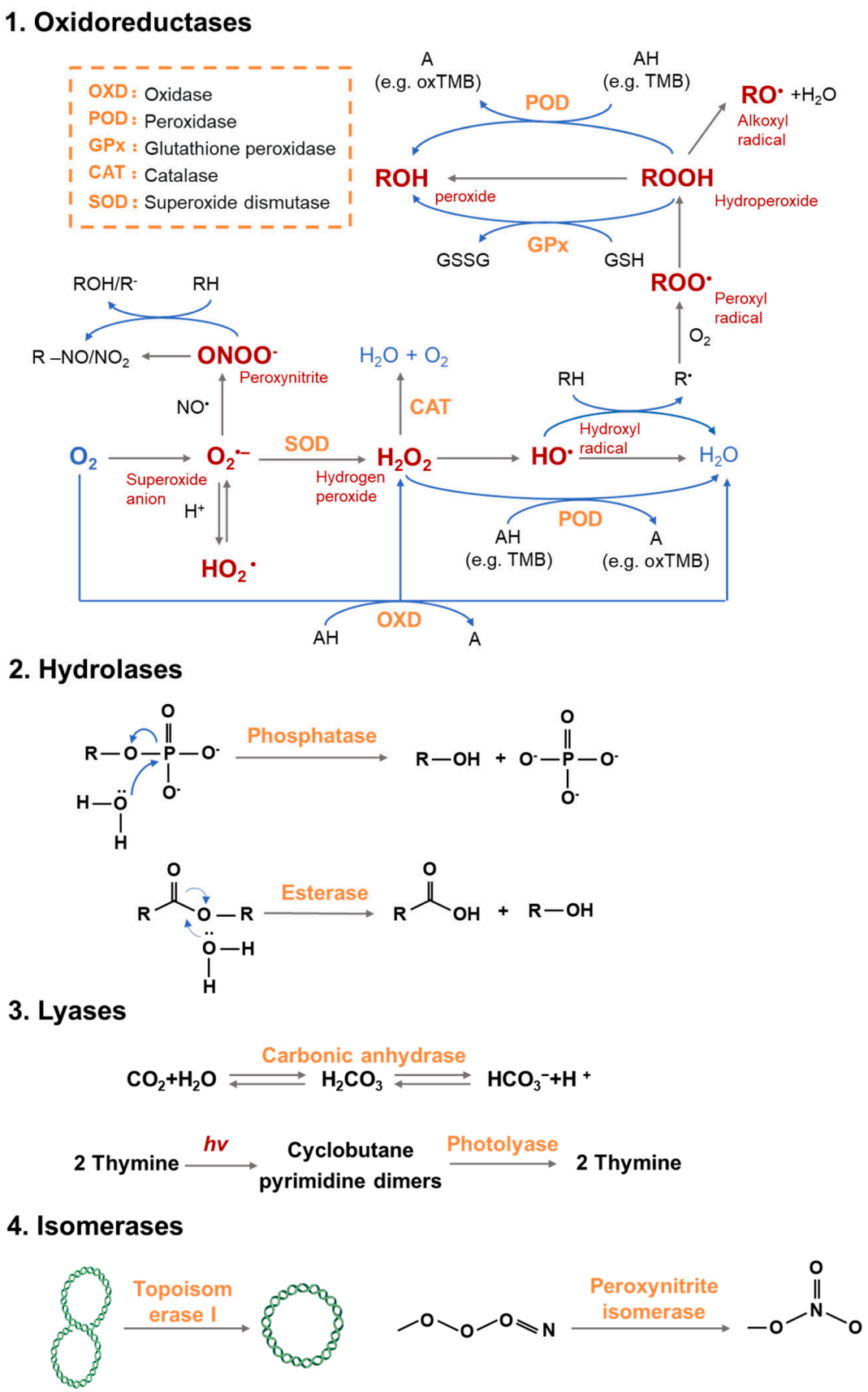

Fig. 2. The chemical basis of reactive oxygen and nitrogen species (RONS) generation, and the examples of chemical reactions involving oxidoreductases-like, hydrolases-like, lyases-like and isomerases-like nanozymes. Adapted from Ref. [16]. Copyright 2019 MDPI.

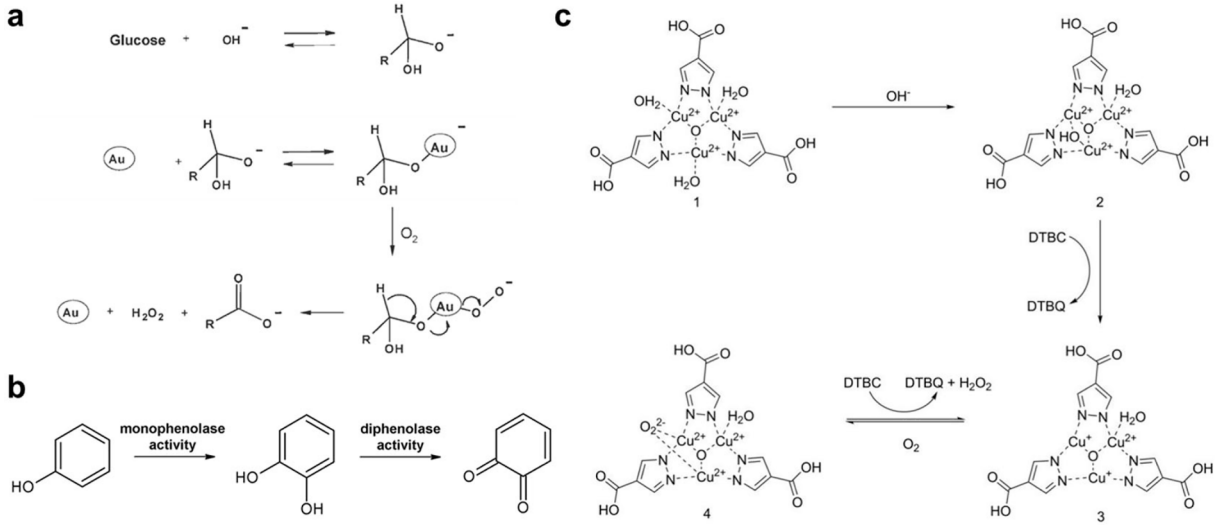

Fig. 3. The diagrammatic representation elucidating the intricate enzymatic mechanism of oxidase or oxidase mimics. (a) Catalytic pathway of Au NPs mimicking GOx. (b) Catalytic process of PPO. (c) Proposed mechanism of catechol oxidase activity of metal-organic framework (MOF)-818. Reprinted with permission from Refs. [38,75] and [41]. Copyright 2006 Wiley-VCH, 2020 Springer Nature and 2020 American Chemical Society.

catalytic sites are all selenocysteine (Sec) residues, and selenium (Se) mediates the redox cycle. In the widely accepted GPx catalytic cycle, selenol (E-Se-H) first reacts with peroxide (H_2O_2/ROOH) to be oxidized to selenate (E-Se-OH) (12). E-Se-OH is considered as the key intermediate, reacting with reduced glutathione (GSH) to yield the formation of selenyl sulfide adduct (E-Se-S-G) (13). Then, another GSH reacts with E-Se-S-G to restore the enzyme to its functional state, forming oxidized glutathione (GSSG) (14).[84] Overall, two equivalent amounts of GSH are oxidized to disulfide and water, while H_2O_2/ROOH is reduced to the corresponding H_2O/ROH (15). Glutathione reductase, in conjunction with its corresponding coenzyme NADPH, can reduce GSSG back to GSH again. After this cycle, E-Se-H will react with the next H_2O_2/ROOH.

E-Se-H + H_2O_2/ROOH → E-Se-OH + H_2O/ROH (12)

E-Se-OH + GSH → E-Se-S-G + H_2O (13)

E-Se-S-G + GSH → E-Se-H + GSSG (14)

Overall: ROOH + 2GSH → GSSG + ROH + H_2O (15)

Inspired by the above catalytic mechanism, Huang *et al.* designed a composite nanozyme (Se@pDA) composed of selenium and polydopamine. Similar to natural GPx, the mechanism of Se nanocomponents catalyzing H_2O_2 decomposition may follow the ping-pong mechanism. The Se component first reacts with H_2O_2 to produce selenium oxide. Then, the intermediate product, selenium oxide, reacts with GSH to restore the Se form, and GSH is oxidized to GSSG. Moreover, the excellent GPx-mimicking ability of Se and the reducing property of polydopamine can exert synergistic antioxidant effects to protect cellular components from oxidative stress.[48] Zhang *et al.* prepared Au nanozymes modified with Se pentapeptide. The N-terminal of the polypeptide is a catalytic group Sec with GPx-like activity, and the C-terminal is a binding group cysteine (Cys). Kinetic analysis results show that the addition of Au NPs changes the catalytic mechanism of the peptide from a ping-pong mechanism to an ordered mechanism. Moreover, the k_{cat}/K_M of GSH and H_2O_2 by selenopeptide-functionalized AuNPs is one order of magnitude higher than that of free selenopeptides. Based on this, it can be speculated that Au NPs can enhance the catalytic activity by restricting the mobility and conformation of the polypeptide, exposing most of the Sec groups to the environment in the presence of substrates GSH and H_2O_2. It is worth mentioning that the K_M value of the substrate H_2O_2 is smaller than that of GSH. Similar to natural GPx, the selenopeptide-functionalized AuNPs only show specific recognition of GSH.[49]

2.1.4. Catalase

The CAT plays an important role in defending against H_2O_2, which is one of the origins of radicals through Fenton reaction or analogous pathways.[85] In the body, CAT found in virtually all aerobic organisms can effectively remove H_2O_2 by decomposing H_2O_2 into O_2 and H_2O, thereby defending cells against oxidative stress (16):[86]

$2H_2O_2 \rightarrow O_2 + 2H_2O$ (16)

As mentioned above, the CAT-mimicking nanozymes have better stability and lower costs than natural CAT. Nowadays, there is a growing anticipation for CAT-mimicking nanozymes to emerge as viable alternatives to natural CAT in many application fields. Dedicated efforts have been undertaken by scientists to investigate the catalytic mechanism of CAT-mimicking nanozymes to achieve this goal. Hitherto, various nanomaterials have been recognized as CAT-mimicking nanozymes, including metal/metal oxides, Prussian blue, MOFs, and N-doped NPs.[87] These nanomaterials also follow Michaelis-Menten kinetic reactions and exhibit high binding affinities for H_2O_2. One of the simple catalytic mechanisms represented by part of metal-based nanozymes is based on the redox reaction by multiple valence switches. Patel *et al.* synthesized ceria (Ce) NPs, which utilized regenerative redox switching between Ce^{3+} and Ce^{4+} ions to selectively remove ROS.[50] However, the catalytic mechanism is not clear for coupled electron transfer, and emphasis should be placed on exploring not only the reaction conditions but also the structural and electronic characteristics of nanozymes in the forthcoming research endeavors. Other metal-based nanozymes like Au [37], Ag[88], and Pd[89] NPs are likely to change their enzyme-like activity in different pH conditions, which is attributed to the different adsorption energies of the molecules under various pH polarizations. Considering the structural and electronic characteristics of CeO_2 NPs, Wang *et al.* demonstrated that oxygen vacancies have a significant impact on the catalytic performance by altering the redox state of Ce,[51] based on the perpetual motion model of CeO_2 catalytic mechanism.[90] Xu *et al.* precisely concluded that there are two major types of mechanisms of CAT-like nanozymes. The difference is whether H_2O_2 chooses to break H-O or the O-O bond preferentially when it gets absorbed.[87]

2.1.5. Superoxide dismutase

Natural SOD is usually composed of protein and metal cofactors, and

can be divided into four types according to different cofactors: CuZn-SOD, Mn-SOD, Fe-SOD, and Ni-SOD.[91] Accompanied by the alternate redox of metal ions in the active site, SOD possesses the ability to catalyze the disproportionation of $O_2^{\bullet-}$, resulting in the production of O_2 and H_2O_2 (19),[92] and the catalytic reaction formula is as follows:

$$M^{(n+1)+} + O_2^{\bullet-} \rightarrow M^{n+} + O_2 \quad (17)$$

$$M^{n+} + O_2^{\bullet-} + 2H^+ \rightarrow M^{(n+1)+} + H_2O_2 \quad (18)$$

$$\text{Overall: } O_2^{\bullet-} + O_2^{\bullet-} + 2H^+ \rightarrow O_2 + H_2O_2 \quad (19)$$

Among them, the metal ion in the oxidized state accepts an electron from $O_2^{\bullet-}$ to convert into a reduced state, and the $O_2^{\bullet-}$ that loses an electron to form O_2 (17). Next, the metal ion in the reduced state transfers an electron to another $O_2^{\bullet-}$, and the $O_2^{\bullet-}$ that has gained the electron combines with two protons to form H_2O_2 (18).

The kinetics of SOD-like nanozymes also follow this ping-pong mechanism, which can effectively eliminate $O_2^{\bullet-}$.[24] Since the SOD-like activity of C60 was reported in the 1990s,[93] SOD-like activity has been found in a variety of metal-doped nanozymes (such as Au, Ag, Pd, Pt, Mn, V, and other metals and their oxides) and carbon dot (CD). For SOD-like nanozymes of metal and alloy, the mechanism predominantly encompasses two parts, namely the protonation of $O_2^{\bullet-}$ and the adsorption rearrangement of $HO_2^{\bullet}$ on the metal surface.

$$O_2^{\bullet-} + H_2O \rightarrow HO_2^{\bullet} + OH^- \quad (20)$$

$$2HO_2^{\bullet} \rightarrow O_2 + H_2O_2 \quad (21)$$

As a Brønsted base, $O_2^{\bullet-}$ reacts readily with H_2O to form $HO_2^{\bullet}$ and OH^- (20). In light of the pronounced exothermicity exhibited by the adsorption of $HO_2^{\bullet}$ onto the nanozyme surface, this easy adsorption shifts the equilibrium towards more $HO_2^{\bullet}$ generation. At the same time, the very low E_{act} means that the adsorbed $HO_2^{\bullet}$ groups are easily converted into O_2 and H_2O_2 (21).[52] For CD nanozymes, the catalytic mechanism was revealed by Gao *et al.* through surface structure adjustment and theoretical calculations. The hydroxyl and carboxyl groups of CDs serve as binding sites, while the carbonyl moieties of CDs serve as the catalytic sites.

$$O_2^{\bullet-} + H_2O \rightarrow HO_2^{\bullet} + OH^- \quad (22)$$

$$HO_2^{\bullet} + O = (C - dot) = O \rightarrow O_2 + HO - (C - dot) - O^{\bullet} \quad (23)$$

$$HO_2^{\bullet} + HO - (C - dot) - O^{\bullet} \rightarrow H_2O_2 + O = (C - dot) = O \quad (24)$$

Consistent with the above process, $O_2^{\bullet-}$ existing in an alkaline environment readily captures a proton from aqueous solution to form $HO_2^{\bullet}$ and OH^- (22). The carbonyl group within the CD transforms the hydroxyl group through the oxidation of $HO_2^{\bullet}$ to O_2 (23). Afterward, π-OH is converted into carbonyl by reducing $HO_2^{\bullet}$ free radicals to H_2O_2 (24).[53]

$O_2^{\bullet-}$ is highly oxidative and can be further metabolized into other ROS, causing oxidative stress. Therefore, as an important antioxidant, SOD-like nanozymes hold immense promise in the realm of preventing and treating a multitude of ROS-related diseases.

2.2. Hydrolases

Hydrolase is a general class of enzyme catalyzing the hydrolysis reaction, or a distinctive type of transferase using water as the receptor for transferred group. Hydrolases are involved in 13 different biotransformation, including esterases, phosphoesterases, amidases, proteases, and glycosidases.[55] Thus, hydrolases have a wide range of substrates.

Given that phosphate bonds exhibit the highest activity among the aforementioned hydrolytic bonds, most studies on hydrolase mimics are centered around this. Elena *et al.* entrapped the organo-phosphorus hydrolase (OPH) protein within a poly ion complex, with a size below 100 nm, to propose hydrolytic nanozymes which have demonstrated remarkable efficacy in safeguarding animals against the detrimental effects of pesticide exposure, specifically paraoxon, as well as the toxic impact of warfare agent known as VX.[94] In addition to specific modification of natural enzymes to enhance their performance, integrating natural metal ion catalytic centers moieties within/onto nanomaterials have been deeply studied, following the discovery of the structural motif featuring a binuclear metal center within the amidohydrolase superfamily. Xia *et al.* directed their attention towards systematically assembling the functional components found in OPH catalytic centers within MOFs including bimetallic Zn^{2+} centers.[54] Oxygen vacancy is also a key factor in catalytic hydrolysis reactions. Lin *et al.* fabricated ceria NPs with abundant and regenerable oxygen vacancy, which exhibit the ability to dephosphorylate phosphor-tyrosine.[95] Except for inorganic-derived nanomaterials, biomolecule-sourced nanozymes (bionanozymes) have been reported by Liang *et al.* Drawing inspiration from the fundamental structure of natural hydrolases, they successfully engineered three hydrolase-mimicking bionanozymes based on oligopeptide, which were able to hydrolyze substrates with side-chains through the self-assembly of histidine-rich heptapeptides induced by Zn.[56] Misfolding and aggregation of proteins leading to forming toxic substances is a common feature of many neurodegenerative diseases covering Alzheimer's disease (AD) and PD. Nanozymes that mimic protease-like activities hold promise for the elimination of amyloid β protein (Aβ), α-synuclein (α-syn) and tau.[96,97] Moreover, the ligand is another essential factor in the design of hydrolytic nanozymes. Different lengths of ligands can yield nanozymes with different active site densities.[98]

However, the extensive substrates range of hydrolases and limited knowledge of their catalytic mechanisms present challenges in the development of new hydrolytic nanozymes. Li *et al.* designed a hydrolytic nanozyme based on a Ce-FMA-MOF structure through integration and induction of previous data.[55] That reminds us of an effective way to design and discover new nanozymes based on machine learning or chemoinformatic models. Hydrolytic nanozymes are expected to be a new field in urgent need of extensive research.

2.3. Lyases

The catalytic mechanism of lyases is to break the chemical bonds such as C-C, C-O, C-N, and C-S. It often participates in reversible reactions, requiring only one substrate for the forward reaction and two substrates for the reverse reaction. Through their cleavage capabilities, lyases change the molecular architecture, and the products often form new double bonds or ring structures. At the same time, the reaction does not require the participation of water or oxygen.

Lyases, including aldolase, hydratase, and deaminase, participate in many different types of biochemical reactions. For example, carbonic anhydrases (CAs) serve as catalysts for the fundamental process of life: the hydration of CO_2 to form bicarbonate and proton. As a subclass of metalloenzymes, the catalytic site within the majority of CAs contains Zn^{2+}.[99] The catalytic mechanism consists of several steps (25):

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+ \quad (25)$$

First, CO_2 binds to the active site, and the OH^- bound by Zn^{2+} carries out a nucleophilic attack on CO_2 to form an enzyme-HCO_3 adduct. Subsequently, due to the weak interaction between HCO_3^- and Zn^{2+} ions, HCO_3^- is replaced by H_2O at the active site. Finally, proton is transferred through the pathway of $W_{Zn\text{-}H2O} \rightarrow W1 \rightarrow W2 \rightarrow$ His64, regenerating OH^- bound to Zn^{2+} (Fig. 4**a**).[100] The CO_2 hydration/ H_2CO_3 dehydration reaction is very slow, while the dissociation or ionization of H_2CO_3 is very rapid and always in equilibrium under physiological conditions.[101] In recent years, to mitigate the greenhouse effect, capturing and sequestering CO_2 by simulating the activity of natural CAs has emerged as a prominent subject of research.[102] Demirsoy *et al.*

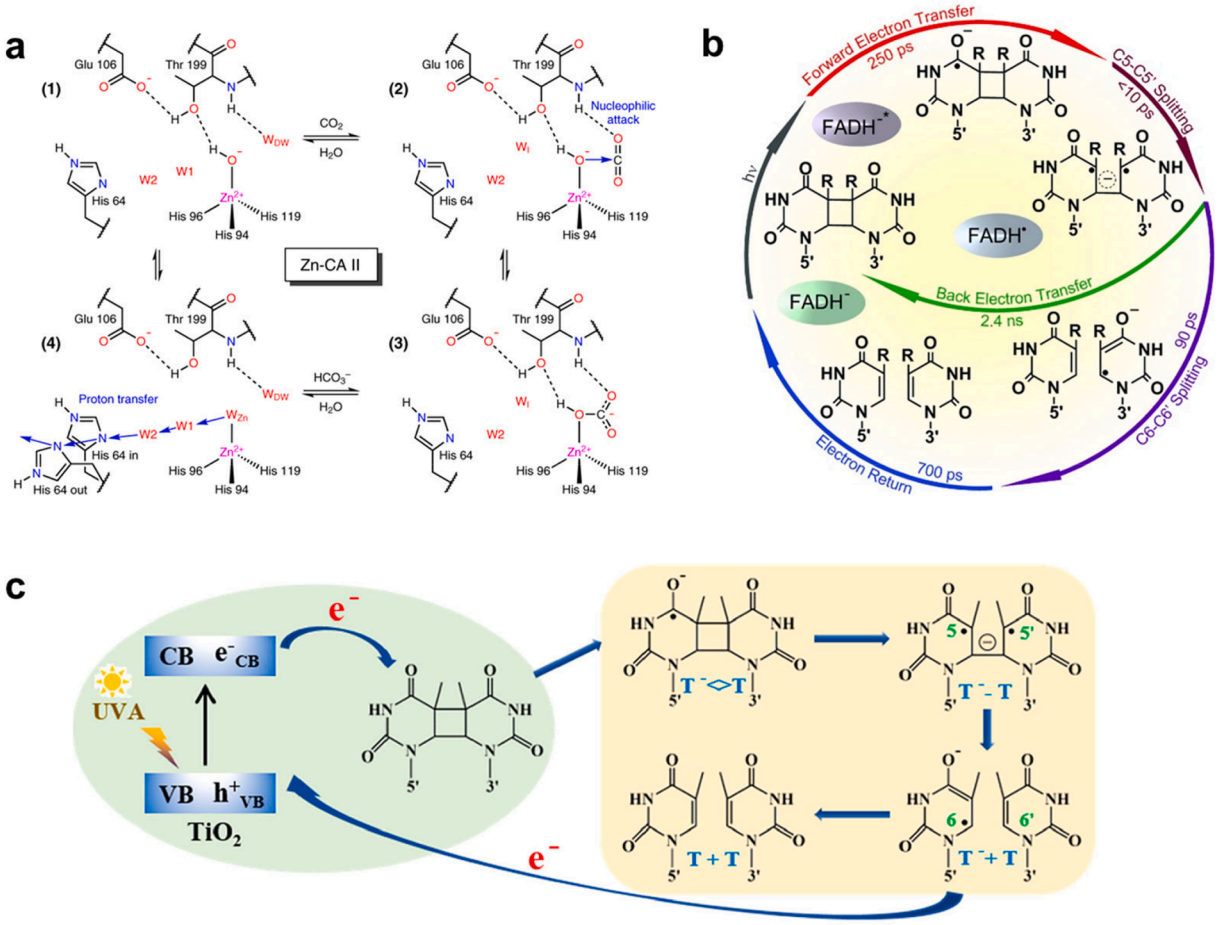

Fig. 4. The diagrammatic representation of the catalytic mechanisms of lyase or lyase mimics. (a) The specific mechanism of CO_2 hydration reaction catalyzed by Zn-CA II. (b) Complete photocatalytic cycle for repairing UV-induced DNA damage by DNA photolyase. (c) The repair mechanism of CPD by TiO_2. Reprinted with permission from Refs. [100,103] and [62]. Copyright 2023 Springer Nature, 2011 National Academy of Science, and 2022 American Chemical Society.

used amino acid-functionalized fullerene nanostructures to mimic different enzymes. It can self-assemble in an aqueous environment to form multiple active sites. The histidine- and threonine-functionalized fullerene derivative HT, which is the most similar nanocatalyst to the α-CA active site containing histidine, threonine, and glutamic acid. Histidine is used to coordinate Zn^{2+} ions to achieve the purpose of water activation, and threonine is responsible for increasing the nucleophilicity of OH^-.[60] A novel zeolitic imidazolate framework (ZIF-8)-based nanozyme was proposed by Chen *et al.* Zn^{2+} with less imidazolium coordination on the outer surface can mimic the active site of human CAII, promoting the generation of OH^- bound to Zn^{2+}, and thus have catalytic properties similar to human CAII.[61]

Additionally, the nanozyme alternatives of DNA photolyases have also been developed. Ultraviolet (UV) irradiation induces the formation of cyclobutane pyrimidine dimers (CPDs) through the linking of two neighboring pyrimidine bases in a DNA strand, thereby blocking the process of replication and transcription.[103] This damage can be repaired by DNA photolyase with $FADH^-$ molecule as an active cofactor.

$$FADH^- \rightarrow FADH^{-}* \quad (26)$$

$$FADH^{-}* + CPD \rightarrow FADH^{\bullet} + T + T^- \quad (27)$$

$$T^- + FADH^{\bullet} \rightarrow FADH^- + T \quad (28)$$

In brief, the photorepair mechanism is that the cofactor $FADH^-$ is excited by absorbing blue light directly or transferring energy in antenna chromophores (26). Excited $FADH^-$* delivers an electron to CPD, which splits into two thymine bases (27). Finally, the electron returns to the cofactor, restoring enzyme activity (28) (Fig. 4**b**).[104] Zhou *et al.* found that TiO_2 can be used as a photolyase mimic to repair CPD damage of DNA. Anatase/rutile mixed phase TiO_2 (P25) has excellent photochemical properties due to high blue light transmittance and electron mobility. The spectral result revealed the maximum repair rate of P25 was 1.59 μM/min. Moreover, the transient spectra and kinetic data indicated that the repair of CPD by P25 is based on the electron transfer mechanism. The photogenerated electrons originating from P25 undergo transfer transition to CPD, resulting in the instability of CPD structure, and then sequentially cracking C5-C5′ and C6-C6′ of cyclobutane. After the CPD is split into T and T^-, the electrons of T^- return to the holes of TiO_2 to complete the photocatalytic cycle and repair the damaged DNA (Fig. 4**c**). In addition to excellent photocatalytic properties, small-sized TiO_2 NPs are easily taken up by cells and have good biocompatibility.[62] Similar to TiO_2, CeO_2 is also a semiconductor and can generate photoelectrons. Under visible light irradiation, CeO_2 can successfully cleave 71.9 % of CPD into monomers, while only 2.4 % of CPD in the control group was cleaved, revealing the photolyase-like activity of CeO_2. Moreover, CeO_2, an antioxidant, can inhibit the generation of ROS, and thus inhibit ROS to completely decompose CPD into fragments and improve the photocatalytic selectivity. In addition, the K_M and k_{cat} indicate that the photocatalytic kinetics of CeO_2 has strong surface-dependent reactivity, and surface defects will effectively enhance the affinity between CeO_2 and CPD.[63]

2.4. Isomerases

Isomerases promote intramolecular rearrangements, which can

catalyze the transformation of substrates into compounds with the same molecular formula but different atomic spatial arrangements. Most reactions are from a single substrate to a single product.[105] Depending on the specific reaction, it can be subdivided into epimerase, cis–trans isomerase, tautomerase, etc. Isomers widely exist in basic substances such as amino acids, sugars, and nucleic acids in nature. Isomerases can realize the interconversion between isomers, for example, alanine racemases catalyze the chiral conversion of L- and D-alanine,[106] glucose isomerases catalyze the interconversion of glucose and fructose.[107]

Unlike natural enzymes, most of the reported nanozymes do not possess the enantioselective ability. Recently, Qu *et al.* grafted multitudinous D- or L-amino acids on the surface of ceria NPs as selectors for chiral recognition, which demonstrated a promising approach for designing stereoselective nanozymes.[108] Carbon-based materials have attracted widespread interest in the development of isomerase artificial mimics due to their easy functionalization.

Li *et al.* designed a chiral CD derived from Cys, which exhibits a resemblance to topoisomerase I and can bind to DNA intercalation via an extended graphitic structure. By generating $^{\bullet}OH$ to cleave the DNA phosphate backbone, it mediates DNA single-strand breaks, thereby regulating DNA topology. Similar to the regulation of gene expression by topoisomerase I, chiral CD can promote gene expression.[64] A heme-functionalized reduced graphene oxide (H-rGO) nanosheet was constructed by Vernekar *et al.* Under physiological conditions, the hybrid nanosheets exhibited significant peroxynitrite isomerization and reduction capabilities. The reduction/isomerization mechanism is similar to that of the iron porphyrin complex.[65]

2.5. Multi-enzyme system

In organisms, a complete biochemical process is often not completed by one enzyme alone, but by several biocatalytic reactions mediated by multi-enzyme complexes that occur simultaneously or sequentially.[109] Although various nanozymes with oxidoreductases-like, hydrolases-like, lyases-like, or isomerases-like properties have been prepared and applied, in order to bridge the gap between nanozyme catalysis and whole-cell catalysis, the development of multi-nanozyme systems that perform multi-step/tandem reactions is indispensable.[110] Currently, the multi-enzyme activities of nanozymes mainly include dual-enzyme activities such as OXD-POD, POD-CAT, and CAT-SOD. In addition, three or more enzyme-like activities are also gradually being developed.

The diagnosis and treatment of brain diseases will greatly benefit from multi-nanozyme systems. As mentioned previously, brain diseases are often caused by the exacerbation of oxidative stress, a process mediated by excessive production of ROS. Antioxidant enzymes possess the capability to scavenge ROS, maintain redox balance, and reduce cell damage and local inflammation caused by oxidative stress. In addition, pro-oxidative enzymes play a crucial role in the detection of neurochemical biomarkers and the treatment of brain tumors.[111] However, when traditional pro-oxidative enzymes and antioxidant enzymes work independently, their functions are relatively simple, and may consequently fall short of the demands for effective diagnosis and treatment of brain diseases. If nanozymes with diverse enzymatic activities are developed, it becomes possible to precisely modulate the levels of ROS within brain cells through synergistic effects and cascade reactions.[110] For example, Singh *et al.* found that Mn_3O_4 NPs can simulate the activities of three types of antioxidant enzymes: SOD, CAT, and GPx. Similar to natural Mn-SOD, Mn_3O_4 NPs first convert $O_2^{\bullet-}$ into O_2 by reducing the metal center (29), and then convert $O_2^{\bullet-}$ into H_2O_2 by oxidizing the metal center (30). The product of the SOD catalytic reaction, H_2O_2, can subsequently serve as a substrate for CAT and GPx catalysis reactions. CAT directly acts on H_2O_2 to produce H_2O and O_2 (31, 32), while GPx uses GSH as a cofactor to convert H_2O_2 into H_2O without producing O_2 (33, 34).[112]

SOD: $Mn(III) + O_2^{\bullet-} \rightarrow Mn(II) + O_2$ (29)

$Mn(II) + O_2^{\bullet-} + 2H^+ \rightarrow Mn(III) + H_2O_2$ (30)

CAT: $Mn(III)\text{-}\ Mn(III) + H_2O_2 \rightarrow Mn(II)\text{-}\ Mn(II) + O_2 + 2H^+$ (31)

$Mn(II)\text{-}\ Mn(II) + H_2O_2 \rightarrow Mn(III)\text{-}\ Mn(III) + H_2O$ (32)

GPx: $Mn(III)\text{-}\ Mn(III) + 2GSH \rightarrow Mn(II)\text{-}\ Mn(II) + GSSG$ (33)

$Mn(II) + H_2O_2 \rightarrow Mn(III) + H_2O$ (34)

Furthermore, under the catalysis of POD, H_2O_2 generates more toxic free radicals, such as $^1O_2$ and $^{\bullet}OH$, which can increase oxidative damage to biological macromolecules. Wei *et al.* synthesized a multi-enzyme nanoreactor (IrRu-GOx@PEG NPs) composed of natural GOx, ultrasmall IrRu alloy NPs with CAT-like and POD-like dual enzyme activities, and surface-modified PEG. First, natural GOx degrades glucose into H_2O_2 and gluconic acid, accomplishing two critical roles: 1) increasing the concentration of H_2O_2 in the tumor microenvironment (TME) and providing substrates for subsequent reactions; 2) cutting off the tumor's nutritional source and promoting tumor cell apoptosis through starvation therapy. Secondly, IrRu NPs catalyze the upstream H_2O_2 to generate O_2 and highly toxic $^1O_2$. Among them, O_2 can relieve hypoxia in the TME, thereby lifting the efficiency limit of GOx-based starvation therapy and forming a virtuous cycle. $^1O_2$ can directly kill tumor cells and inhibit tumor growth.[113]

Designing nanozyme systems with multiple types of enzyme activities will help further advance the detection of analytes. This approach not only enables the fabrication of cascade sensing systems, but also expands the range of analytes and improves overall detection performance.[114] For example, Wu *et al.* synthesized FeCo co-doped carbon spheres (FeCo@C) with intrinsic POD and OXD-like activities. The multi-enzyme activity of FeCo@C is affected by external environments such as pH. After catalyzing for 6 min in a pH 3.6 environment, FeCo@C showed high OXD-like activity and can oxidize TMB to oxTMB, resulting

Table 3
A summary of nanozymes for brain disease diagnosis.

Nanozymes	Activities	Neurochemical biomarkers detected	Detection range (μM)	Detection limit (μM)	References
INAzyme (GOx/hemin@ZIF-8)	POD	Glucose	100–1000	1.7	[120]
AuNPs@MIL-101@GOx	POD	Glucose & Lactate	10–200	4.2 5.0	[121]
V_2O_5 nanobelts	POD, GOx	Glucose	200–5000	0.33	[122]
Hemin-doped HKUST-1/rGO	POD	Dopamine	0.03–10	0.0327	[125]
ZIF-67/$Cu_{0.76}Co_{2.24}O_4$ NSs	POD, SOD, GPx, Laccase	3,4-dihydroxyphenylacetic acid	0.5–20	0.15	[126]
ZIF-L-Co-10 mg Cys	Ascorbate oxidase, Laccase, Glutathione oxidase	Uric acid	0.2–50	0.067	[128]
PBA NC	LOx	Hydrogen sulfide	0.1–20	0.033	[106]
MIL-101(Fe)	POD	ACh & Ch	0.1–10 0.01–100	0.020 8.9	[132]

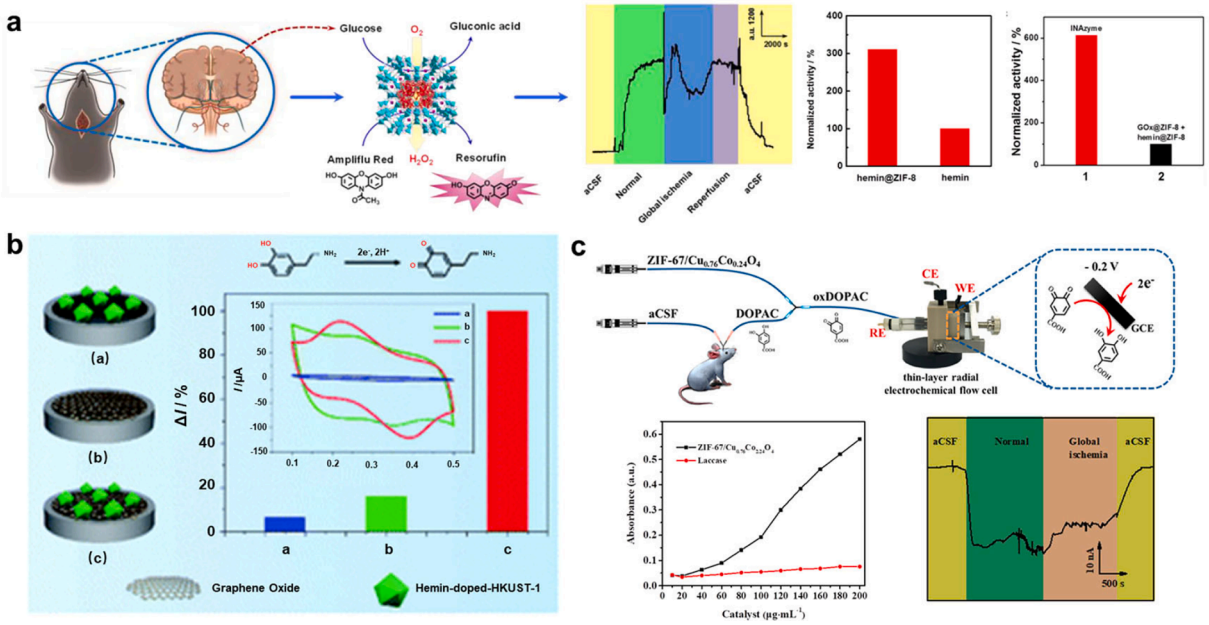

Fig. 5. Nanozymes for the detection of neurochemicals to diagnose brain diseases. (a) Uninterrupted real-time monitoring of cerebral glucose by an integrated sensing platform utilizing INAzyme. (b) Detection of DA by an ultrasensitive electrochemical sensor based on Hemin-doped-HKUST-1/rGO. (c) Monitoring of DOPAC by an online electrochemical detection platform based on the ZIF-67/$Cu_{0.76}Co_{2.24}O_4$ NSs with laccase-like activity. Reproduced with permission from refs [120,125] and [126]. Copyright 2021 Royal Society of Chemistry and 2016, 2020 American Chemical Society.

in color changes. However, FeCo@C showed higher POD-like activity after catalyzing for 3 min in a pH 4.4 environment. By controlling the pH value to avoid mutual interference of the dual enzyme activities, dual detection of hydroquinone and H_2O_2 is achieved.[115] Therefore, the emergence of multi-nanozyme systems brings great hope to the further development of the field of diagnosis and treatment of brain diseases.

3. Nanozyme-based diagnosis of brain diseases

Monitoring neurochemical biomarkers assumes paramount significance in unraveling the functions of these substances within the physiological and pathological phenomena of the brain, as well as for the diagnosis of various brain diseases. Therefore, online *in vivo* detection systems based on electrochemical or optical detection are current research hotspots. Based on OXD/POD-mimicking activities, nanozymes have been explored for monitoring single or multiple brain neurochemicals (Table 3).

The human brain, a mere 2 % of body mass, consumes approximately 20 % of the energy harnessed from glucose metabolism.[116,117] In addition to being the main energy source, glucose also participates in significant activities such as the synthesis of neurotransmitters, learning and memory building, as well as pathologic conditions including oxidative stress.[118] Thus, disturbances in glucose levels may lead to cognitive impairment, memory impairment, and other disorders. Previous studies have designed biosensors based on GOx and HRP. In this biosensing system, glucose is oxidized to H_2O_2 by GOx (35), and then TMB or other organic substrates react with H_2O_2 under the catalysis of HRP to generate color products (36).[119].

$$\text{glucose} + O_2 \rightarrow \text{gluconic acid} + H_2O_2 \quad (35)$$

$$2AH + H_2O_2 \rightarrow 2A + 2H_2O \quad (36)$$

Nanozymes with POD-like activity have been used as HRP substitutes due to their remarkable advantages. By embedding heme and GOx in ZIF-8 nanostructures, Cheng *et al.* prepared integrated nanozymes (GOx/hemin@ZIF-8). In contrast to free heme, the POD-mimicking activity of hemin@ZIF-8 was increased by more than 3 times. This was because free heme tended to form aggregates, whereas the ZIF-8 maintained heme as a monomer. Moreover, the significant enhancement of the enzyme-mimicking properties is attributed to the elevated specific surface area and the enrichment effect conferred by the ZIF-8. Notably, the co-encapsulation of GOx and heme within the ZIF-8 mimicked multiple enzymes confined in subcellular compartments in biological systems. This nanoscale proximity effect significantly improved the enzyme stability and synergistically enhanced the catalytic activity by lowering diffusion hindrance and reducing the degradation of highly reactive intermediates. In addition, the online detection system composed of integrated nanozymes and microdialysis technology can continuously monitor the dynamic fluctuations in glucose levels within the striatal region of the brain after ischemia/reperfusion (Fig. 5**a**). Other enzymes may also be applied in this strategy, such as LOx.[120] By combining the surface-enhanced Raman scattering (SERS) activity and catalytic properties of Au NPs, the same team designed Au NPs@MIL-101-based nanozymes. Due to the POD-like activity, it can catalyze the conversion of Raman inactive reporter molecules (i.e., leucomalachite green) into active reporter molecules (i.e., malachite green). Then, the nanozymes were assembled with GOx and LOx to further construct integrated nanozymes, which demonstrated remarkable efficacy in the real-time monitoring of glucose and lactate dynamics closely related to normal and abnormal states within the brains of living animals.[121] The multi-enzyme activity exhibited by many nanozymes provides a new idea for glucose monitoring which requires the participation of natural GOx. Ding *et al.* found that V_2O_5 nanoribbons have bifunctional enzyme-mimicking capabilities (GOx and POD), and utilized the tandem enzymatic activity of V_2O_5 nanoribbons to continuously monitor glucose in the rat brain. This method has exceptional selectivity, heightened sensitivity, high stability, and a broad dynamic detection range (0.2 to 5 mM),[122] which further breaks the traditional colorimetric detection process and truly realizes glucose detection without natural enzymes.

Furthermore, through rational design and regulation of the activity of nanozymes, the types of neurochemicals detected online are being continuously expanded. As a prominent catecholamine neurotransmitter, DA plays an important role in neuromodulation encompassing cognition, motor coordination, motivation, and reward.[123] It has

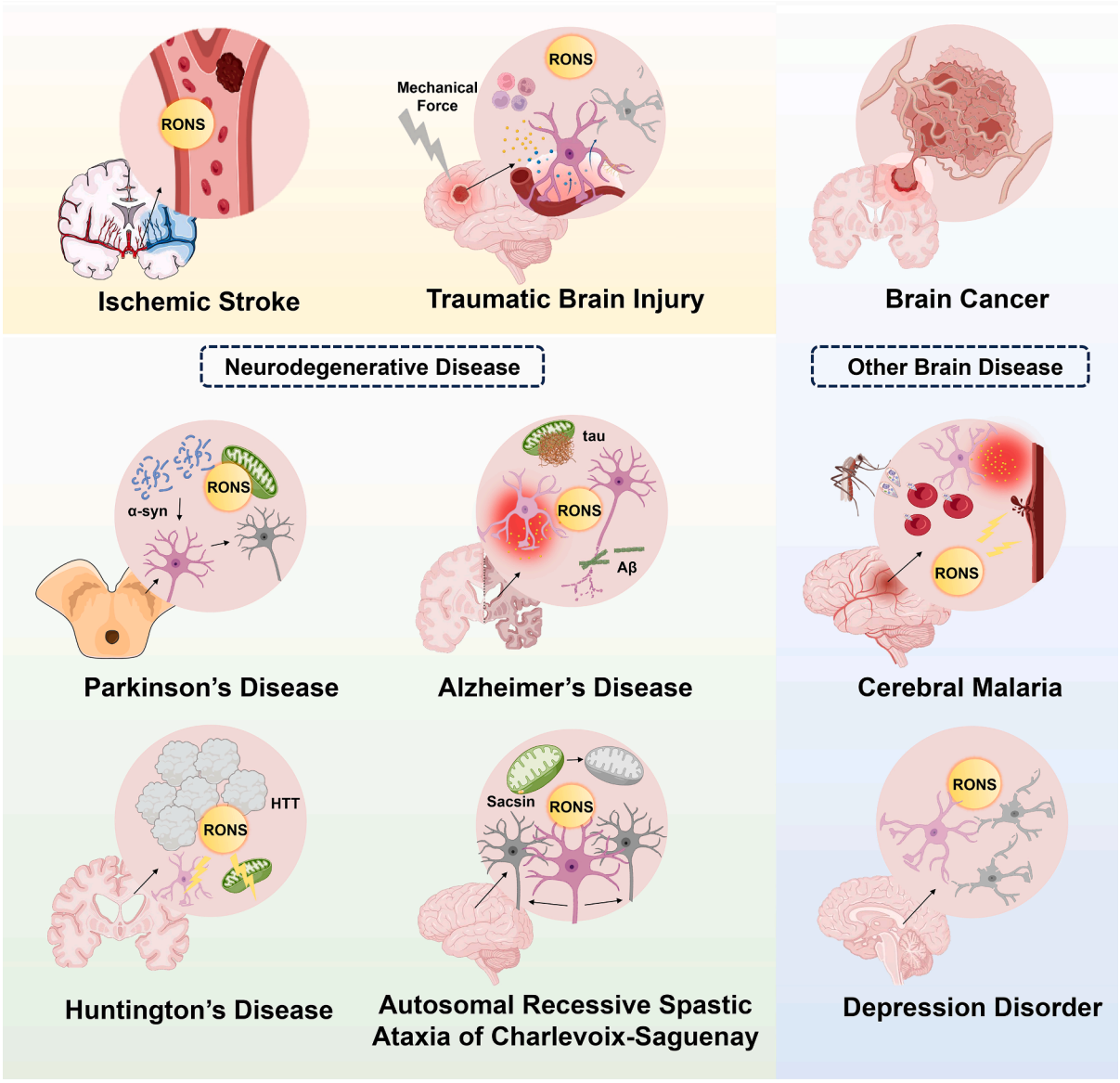

Fig. 6. Schematic diagram summarizing the pathological features of different brain disorders, including IS, TBI, neurodegenerative diseases (PD, AD, Huntington's disease (HD), and autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) and other brain diseases (brain cancer, CM, and depression disorder). This Figure created with BioRend.com and Servier Medical Art (http://smart.servier.com).

been implicated in various brain diseases including PD, schizophrenia, depression, and attention deficit hyperactivity disorder. For example, PD ensues from the gradual degeneration and loss of dopaminergic neurons.[124] Therefore, achieving sensitive, accurate, and low-cost detection of DA assumes paramount significance in the clinical diagnosis of brain diseases. Kang *et al.* synthesized novel multifunctional MOF nanozymes doped with hemin, and further composited them with reduced graphene oxide (rGO) to fabricate an ultrasensitive electrochemical sensor for DA detection. The catalytic current of HKUST-1/rGO/GCE doped with hemin exhibited a remarkable enhancement, surpassing that of rGO/GCE and Hemin-doped-HKUST-1/GCE by approximately 6.3 times and 16 times, signifying the synergistic catalytic ability (Fig. 5**b**). Based on the improved catalytic activity, the sensor has a higher sensitivity (1.224 μA μM^{-1}) and a lower detection limit (3.27×10^{-8} M).[125] As an important metabolite of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) within the cerebrospinal fluid of PD patients is markedly lower than that of normal controls, which is consistent with severe striatal DA depletion.[126,127] Liu *et al.* prepared ZIF-67/$Cu_{0.76}Co_{2.24}O_4$ NSs by a one-step alcohol-hydrothermal method using ZIF-67 as a template and achieved continuous and near real-time response DOPAC measurement. Different from the series of studies above which mainly used the POD-like activity of nanozymes to realize real-time detection of neurochemicals *in vivo*, this study was the basis of the laccase-mimicking activity to monitor DOPAC. The combination of online electrochemical system with microdialysis technology enabled the acquisition of DOPAC concentration in cerebral dialysate both pre- and post-ischemia. The results showed that when the rats were in ischemia for 30 min, the current dropped notably, which corresponded to a decrease in DOPAC concentration from 12.3 ± 1.8 μM (n = 3) before ischemia to 9 ± 1.2 μM (n = 3) (Fig. 5**c**).[126] The online electrochemical system and optical detection platform built by this team have also realized the online continuous detection of brain uric acid and hydrogen sulfide,[128,129] which provided new ideas for the diagnosis of brain diseases, including afflictions like injury and neurodegenerative diseases.

Another important neurotransmitter, ACh, is closely related to neurotransmission and modulation.[130] Its precursor choline (Ch) is not only an essential nutrient for the body, but also a neuroprotective

agent for maintaining the normal development of the brain, which is beneficial to alleviate age-related memory decline and cognitive impairment.[131] Abnormal levels of Ch and ACh can induce a variety of brain diseases, including Down syndrome, PD, AD, and schizophrenia. Therefore, the quantitative analysis of Ch and ACh holds immense importance in the diagnosis of related brain diseases. A fluorescent biosensor utilizing MIL-101(Fe) nanozyme as its core component was developed by Gou *et al.* MIL-101(Fe) with outstanding POD-mimicking activity can be used to detect Ch and ACh after coupling with acetylcholinesterase (AChE) and choline oxidase (ChOx). The cascade catalytic reaction is mainly divided into three steps. AChE catalyzes the hydrolysis of ACh into acetic acid and Ch (37). Subsequently, ChOx catalyzes the cleavage of Ch to produce H_2O_2 (38). Finally, MIL-101(Fe) catalyzes the decomposition of H_2O_2 to generate highly active $^{\bullet}OH$, and oxidizes the non-fluorescent substrate terephthalic acid to the highly fluorescent product 2-hydroxyterephthalic acid (39).[132]

acetylcholine → choline + acetic acid (37)

choline → betaine + H_2O_2 (38)

H_2O_2 + terephthalic acid → H_2O + 2-hydroxyterephthalic acid (39)

In the precise analysis of biomolecules, enhancing the catalytic efficiency of nanozymes remains necessary. Therefore, some studies have combined defect engineering with nanozymes. Defects have long been considered undesirable features of crystals because disruptions in the periodic arrangement of atoms lead to disturbances in the geometry and electronic structure. However, with progressively better understanding of catalytic processes, defect engineering has emerged as a practical approach for adjusting the structure and properties of nanomaterials. In most cases, the defects directly assume the role of active centers or co-catalytic sites. Moreover, the embeddedness of defects may activate nearby atoms to become active sites through the deformation of local geometry and electronic structure, which effectively reduces the gap in enzymatic activity between nanozymes and natural enzymes.[133] By doping Cys, Ren *et al.* introduced structural defects into ZIF-L-Co. When doped with 10 mg Cys, the multi-enzyme activities of ZIF-L-Co were increased several times. The researchers conducted multiple experiments to explore the origins of high activity, and the conclusions can be divided into the following aspects: 1) Cys with high affinity for Co^{2+} disrupts the equilibrium between Co^{2+} and N within ZIF, causing lattice distortion, and bringing abundant coordinative unsaturated sites. 2) The surface area increases, which promotes the adsorption of substrates on the surface of the material. The detection system utilizing ZIF-L-Co-10 mg Cys was able to monitor UA levels in the striatum of mouse brains after ischemia–reperfusion injury.[128]

4. Nanozyme-based treatment of brain diseases

Thanks to their scalability and designability, nanozymes show great potential in biomedicine. Researchers designed different types of nanozymes to effectively treat brain diseases by improving brain targeting, enhancing the activity of antioxidant enzymes, inhibiting inflammatory reactions, or achieving combined reactions (Fig. 6).

4.1. Ischemic stroke

As the first leading cause of disability and the second leading cause of death worldwide, stroke affects over 101 million people currently.[134] It can be broadly divided into IS (71 %) and hemorrhagic stroke (29 %).[2] IS generally refers to cerebral ischemia and hypoxia caused by embolism or thrombus blocking cerebral blood vessels.[135,136] Clinically, vascular recanalization is often achieved through intravenous thrombolytic therapy or mechanical thrombectomy to save the ischemic penumbra.[137] However, after ischemia/reperfusion, numerous RONS are produced, including $O_2^{\bullet-}$, H_2O_2, $^{\bullet}OH$, nitric oxide ($^{\bullet}NO$), and peroxynitrite ($ONOO^-$).[138] They mediate oxidative stress and instigate multiple immoderate inflammatory reactions, which impair neurological function, and thus seriously affect the prognosis of patients.[139] Specifically, RONS lead to irreversible structural damage and dysfunction of brain tissues by strongly oxidizing proteins, nucleic acids, and lipids.[140] Besides, RONS activate microglia and stimulate inflammatory cells to secrete interleukin-1β, interleukin-6, and other cytokines, thereby mediating inflammation and immune response.[141] Endogenous antioxidant enzymes are excessively consumed during disease progression and are difficult to adequately supplement externally due to the low stability and high production costs of natural enzymes.[138] For this reason, a series of free radical scavengers, such as edaravone (Eda), have been used in IS as neuroprotective agents. Despite their beneficial effects, low bioavailability, poor selectivity, poor BBB permeability, and severe side effects have greatly limited their development.[142,143] Compared with these typical antioxidants, nanozymes have higher catalytic activity, bioavailability, and stability, resulting in extended residence time in tissues. Therefore, nanozymes have emerged as a viable strategy for treating IS.

Oxygen vacancies on the surface of the ultrasmall ceria nanozymes allow reduced state (Ce^{3+}) and oxidized state (Ce^{4+}) to coexist, thereby scavenging RONS through electron transfer between Ce^{4+} and Ce^{3+}.[144,145] In 2012, ceria nanozymes with SOD and CAT mimetic activities were prepared by Kim *et al.* to prevent ischemia by scavenging ROS and reducing apoptosis.[146] However, ultra-small ceria nanozymes exhibit a short half-life in blood circulation, and easily agglomerate. In addition, the accumulation of nanozymes in the brain may disrupt BBB and cause neurological dysfunction. Hence, it is of great significance to accomplish BBB penetration and protection simultaneously. Bao *et al.* designed EA/P-CeO_2 to enhance brain accumulation through receptor-mediated transcytosis. EA/P-CeO_2 relied on the enzyme-mimicking activity of CeO_2 and loaded Eda to synergistically eliminate ROS for effective treatment of IS.[147] He *et al.* adopted another strategy. They encapsulated CeO_2 NPs with ZIF-8 to change the surface properties of CeO_2 and prevent its aggregation. Moreover, ZIF-8 demonstrates notable efficacy in prolonging blood circulation time and improving the penetration of BBB. CeO_2@ZIF-8 effectively inhibited oxidative damage to brain neurons as well as damage caused by inflammation.[148]

The ratio of Ce^{3+} to Ce^{4+} and the particle size greatly limited the catalytic activity of CeO_2 NPs.[149] Therefore, other nano-antioxidants (such as MnO_2, Prussian blue, Fe_3O_4, CDs, and melanin) have been successively developed for IS treatment.[138,150,151] Using appropriate strategies to modify nanozymes to improve their brain targeting is one of the research directions. Zhao *et al.* designed a manganese dioxide nanozyme (Eda-MnO_2@Tf, EMT) targeting transferrin (Tf) and loading with Eda. EMT exhibited excellent brain targeting and strong ROS scavenging capability. Besides, the Mn^{2+} released in the weakly acidic environment could serve as a means of monitoring therapeutic progress through magnetic resonance imaging (MRI).[30] Mesoporous Prussian blue nanozymes coated on neutrophil-like cell membranes (MPBzyme@NCM) were designed by Feng *et al.* One of the pathological hallmarks after stroke is the interplay between leukocytes and inflamed microvascular endothelial cells (ECs) in the brain. Inspired by this, the transfer of neutrophil membranes to the surface of nanozymes could potentially enhance their specific targeting towards inflamed microvascular ECs in the brain, thereby enabling their entry into the damaged brain and subsequent phagocytosis by microglia. MPBzyme@NCM mediated the long-term treatment of IS by driving microglial polarization to M2, reducing neutrophil recruitment, and inhibiting neuronal apoptosis (Fig. 7**a**). This research work explored a new method for nanozymes to break through the BBB. However, how to further improve the delivery efficiency of nanozymes into the damaged brain through this entry method still needs to be studied.[152] Another research direction is to design nanozymes with elevated antioxidant activity. Liu *et al.* designed Co-Fe_3O_4 co-doped nanozymes to target RONS in the

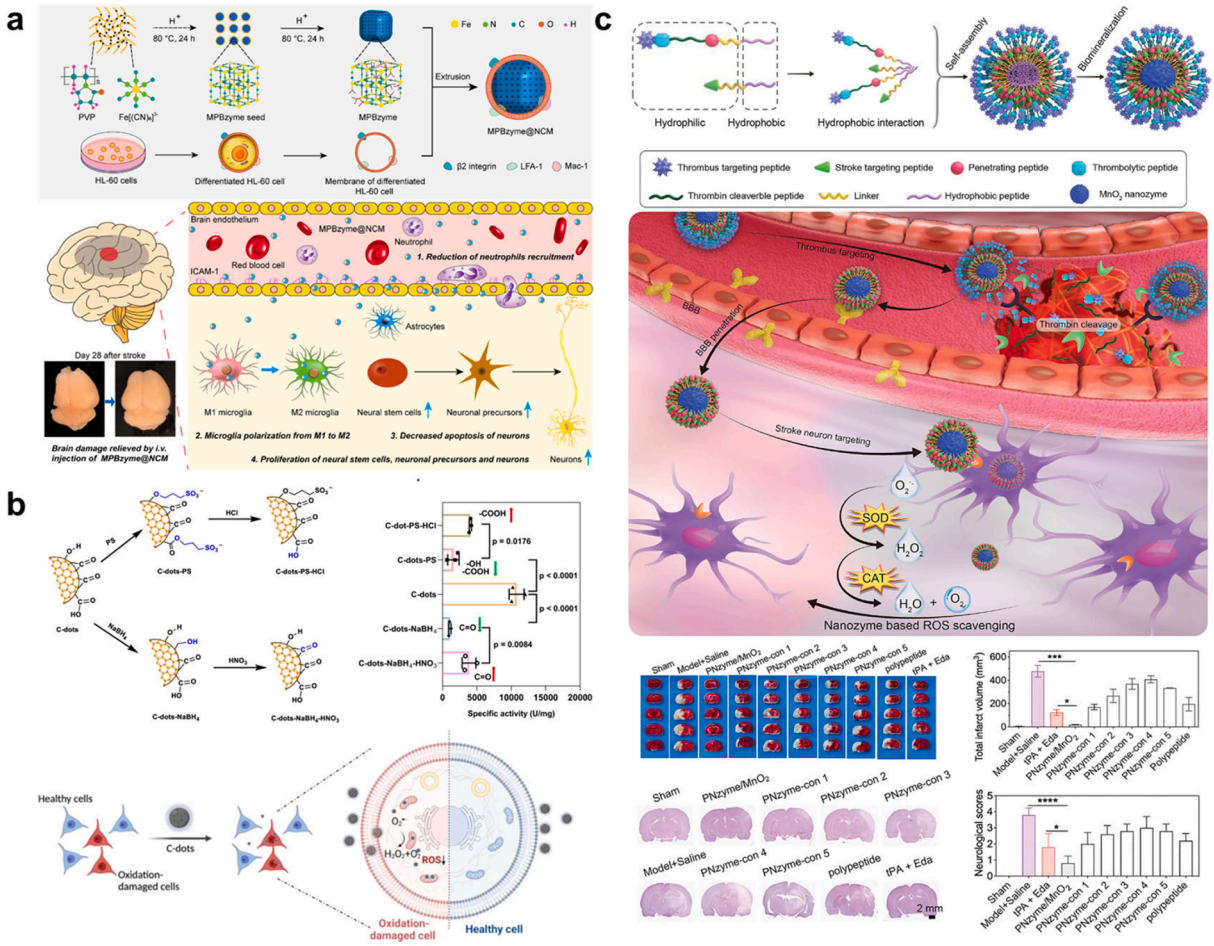

Fig. 7. Strategies aimed at enhancing the therapeutic efficacy of nanozymes for IS. (a) Improvement in brain targeting. MPBzyme@NCM targeting inflamed brain microvascular ECs. (b) Enhancement of antioxidant activity. C-dots with high SOD-mimicking activity obtained by adjusting surface functional groups. (c) Combination or cascade therapy. PNzyme/ MnO_2 with the ability to both dissolve thrombus and scavenge ROS. Reprinted with permission from Refs. [152,53] and [154]. Copyright 2021 American Chemical Society, 2023 Springer Nature, and 2021 Wiley-VCH.

ischemic brain. When compared with Fe_3O_4, the defect-engineered Co-Fe_3O_4 showcased a 100-fold increase in affinity towards H_2O_2.[153] Gao *et al.* prepared CD nanozymes, which exhibited SOD-like activity greater than 10,000 U/mg under appropriate reaction conditions and raw material conditions. The results of surface structure adjustment combined with theoretical calculations show that enhancing the abundance of oxygen-containing functional groups including hydroxyl, carboxyl, and carbonyl on the surface of CD is beneficial for the improvement of SOD-like activity. In addition, CD nanozymes can target the interior of oxidative damage cells and effectively scavenge intracellular ROS. In a mouse model of IS, CD nanozymes can specifically accumulate in damaged brain regions and reduce stroke-induced oxidative damage (Fig. 7**b**).[53]

The above-mentioned nanozymes mainly play a neuroprotective role in alleviating the secondary injury caused by massive RONS generated by reperfusion. It is worth mentioning that Wang *et al.* reported innovative peptide-templated manganese dioxide nanozymes (PNzyme/ MnO_2), which have both neuroprotective and thrombolytic abilities. Self-assembling polypeptides contain a variety of functional motifs. The fibrin-binding sequence specifically targets thrombi in ischemic brain regions, and thrombin activates the thrombin-recognized, and cleaved sequence as a functional switch initiates the activity of the thrombolytic sequence, followed by secondary and tertiary targeting (Tf-mediated BBB targeting sequence and apoptotic neuron targeting sequence) to guide the further localization of IS tissue to scavenge ROS. Subsequently, the nanozyme that possesses the cascade catalytic activity of SOD and CAT can effectively decompose ROS into nontoxic O_2 and H_2O, thus protecting the organisms from excessive ROS (Fig. 7**c**).[154]

4.2. Traumatic brain injury

TBI refers to temporary or even permanent damage to brain function or structure caused by external mechanical force. The pathophysiology of TBI is divided into two phases, primary and secondary injury. When the brain suffers a primary mechanical injury, neurons and glial cells respond to the injury, triggering various physiological and biochemical processes within the organism, which further leads to lasting secondary damage, including BBB disruption, neuroinflammation, cerebral edema, and ischemia hypoxia. In the complex cascade of secondary damage mechanisms, oxidative and nitrosative stress which arises from the accumulation of RONS is a key factor.[155] Mitochondrial dysfunction leads to O_2 leakage, which generates ROS under the catalysis of NADPH oxidase. In addition, hyperactivation of N-methyl-d-aspartate receptors and Ca^{2+} influx lead to the excessive generation of RNS.[156] RONS spread into the surrounding normal brain, oxidizing nucleic acids, proteins, and lipids.

As possessing powerful antioxidant activity, nanozymes have demonstrated encouraging potential for utilization in the treatment of TBI. The excretion of inorganic nanozymes is slow, while nanozymes with larger sizes tend to accumulate non-specifically in healthy organs. Therefore, some researchers have turned to exploring alternative solutions of small organic nanozymes for brain damage. Mu *et al.* developed

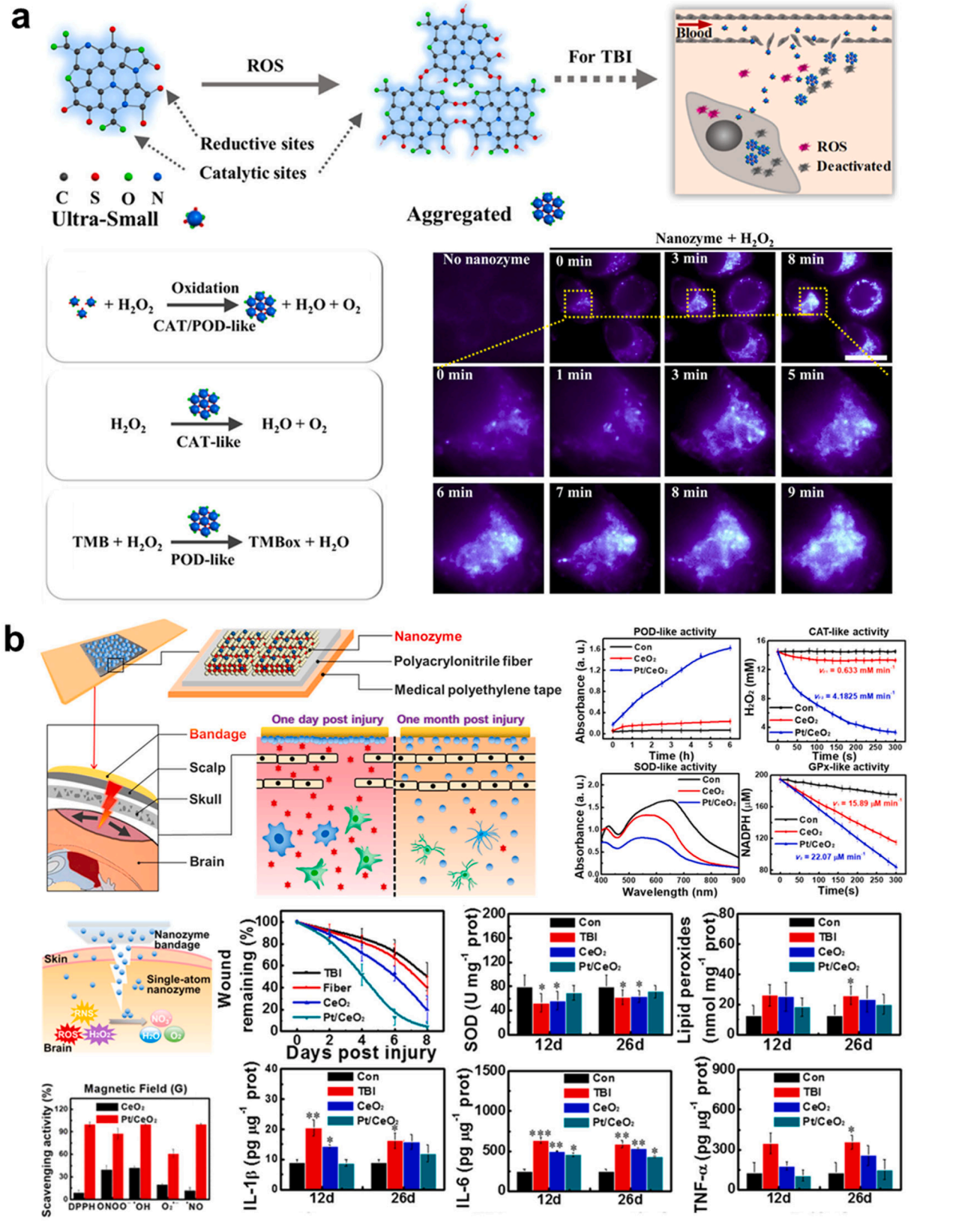

Fig. 8. Nanozymes for the treatment of TBI. (a) Aggregation of ROS-induced nanozymes for the treatment of TBI. (b) A non-invasive bandage for treating brain trauma utilizing single-atom catalytic nanozymes. Reprinted with permission from Refs. [158] and [159]. Copyright 2019 American Chemical Society.

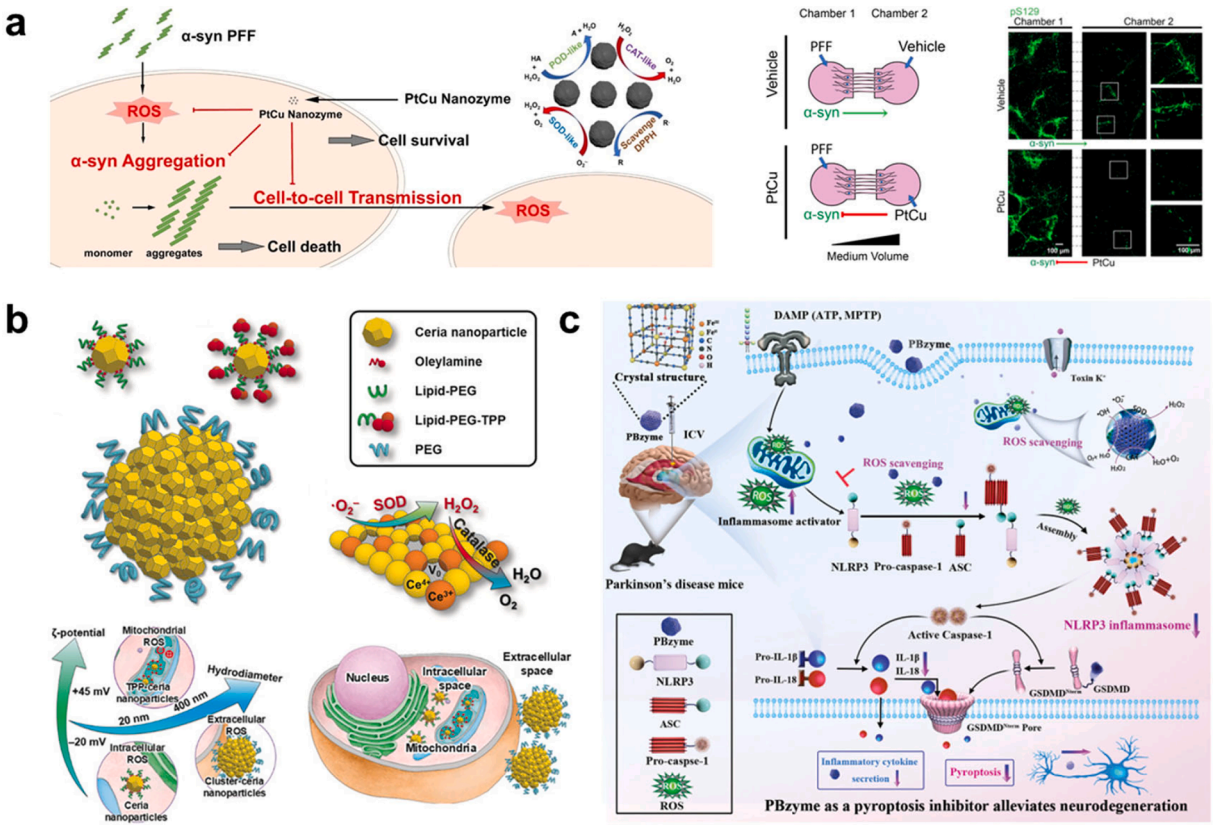

Fig. 9. Nanozymes for the treatment of PD. (a) Inhibition of α-syn pathology. An overview of PtCu nanozymes scavenging ROS and mitigating the pathological effects induced by α-syn. (b) ROS scavenging. Schematic illustration depicting ceria NPs scavenge ROS in response to their cellular distribution. (c) Inhibition of neuroinflammation. Mechanism of PBzyme as a pyroptosis antagonist to inhibit neuroinflammation and protect PD neurons. Reprinted with permission from Refs. [165,169] and [170]. Copyright 2021 Elsevier, 2018 and 2022 Wiley-VCH.

ultra-small carbogenic nanozymes. After intravenous injection, nanozymes exhibited efficient elimination of over-produced RONS in acute TBI-induced brain tissue. Unlike the above-mentioned ultrasmall ceria nanozymes that easily aggregate *in vivo*, the ultrasmall carbogenic nanozymes showed effective renal clearance at high doses.[157] He *et al.* successfully synthesized an ultrasmall (~3 nm) organic nanozyme using the microwave-heating method of lysine and GSH. Upon exposure to free radicals, it can gradually aggregate to 75–100 times its original size, and undergo disintegration into smaller entities through the action of NADPH-glutathione reductase (Fig. 8**a**). This aggregation reversibility was beneficial to promote excretion following the recovery from TBI.[158]

Compared with the previous intravenous route of nanozyme, the nanozyme-based wound dressing provides a new non-invasive treatment for TBI. Traditional bandages are mainly used to relieve pain, pressurize to stop bleeding, and protect wounds from environmental influences. However, after long-term exposure at room temperature, the antibiotics, antioxidants, and enzymatic debriding agents on the surface of the bandage are prone to failure, and it is challenging to promote wound healing. Yan *et al.* ingeniously devised a non-invasive treatment approach for trauma by developing a single-atom Pt/CeO_2-rich bandage. Dispersed Pt single atoms enhanced the multienzyme activity of CeO_2 clusters by 3–10 times and the RONS-scavenging activity by 2–10 times because Pt single atoms with oxygen vacancies can provide active catalytic sites. Experiments showed that the bandage can reduce oxidative stress and inflammatory response indicators. Compared with traditional intravenous administration for brain injury, Pt/CeO_2 nanozyme-based bandages seem to show great potential due to their non-toxic and sustained multi-catalytic processes (Fig. 8**b**).[159] Subsequently, the research team kept this idea and further designed an enhanced catalytic patch utilizing Cr-doped CeO_2 nanozymes.[160] Compared with the aforementioned research, the preparation procedure of nanozyme was changed from a hydrothermal process to a coprecipitation process. Among CeO_2 nanozymes doped with various metallic elements, the Cr/CeO_2 nanozymes showed the best catalytic activity.

The catalytic process *in vivo* is complex, so nanozymes with physiological environment preference are particularly important for treating TBI. Nonetheless, the majority of nanozymes exhibit suboptimal catalytic activity in the neutral physiological environment. The aforementioned Pt/CeO_2 nanozyme has an acidic environment preference, exhibiting POD-mimicking activity in an acidic environment while CAT-mimicking activity in neutral and alkaline environments. Mu *et al.* demonstrated a trimetallic nanozyme that exhibited optimal catalytic performance in a physiological environment attributed to the lattice distortion and exposure of catalytic centers. At the same time, the multienzyme mimetic activity endowed it with multiple antioxidant properties, which can improve mice's post-brain injury survival percentage and significantly alleviate neuroinflammation.[161]

4.3. Neurodegenerative disease

4.3.1. Parkinson's disease

PD, ranking as the second most prevalent neurodegenerative disease, presents with abnormal motor symptoms (tremor, motor retardation, stiffness, abnormal gait, and postural instability) and a series of non-motor complications (cognitive, psychiatric, sleep, and sensory disturbances).[162] PD involves different types of neurons populations distributed across multiple brain regions, the most important one being the DA neurons in the Substantia Nigra compact (SNc). The α-syn, a characteristic constituent of the Lewy body in DA neurons, is misfolded

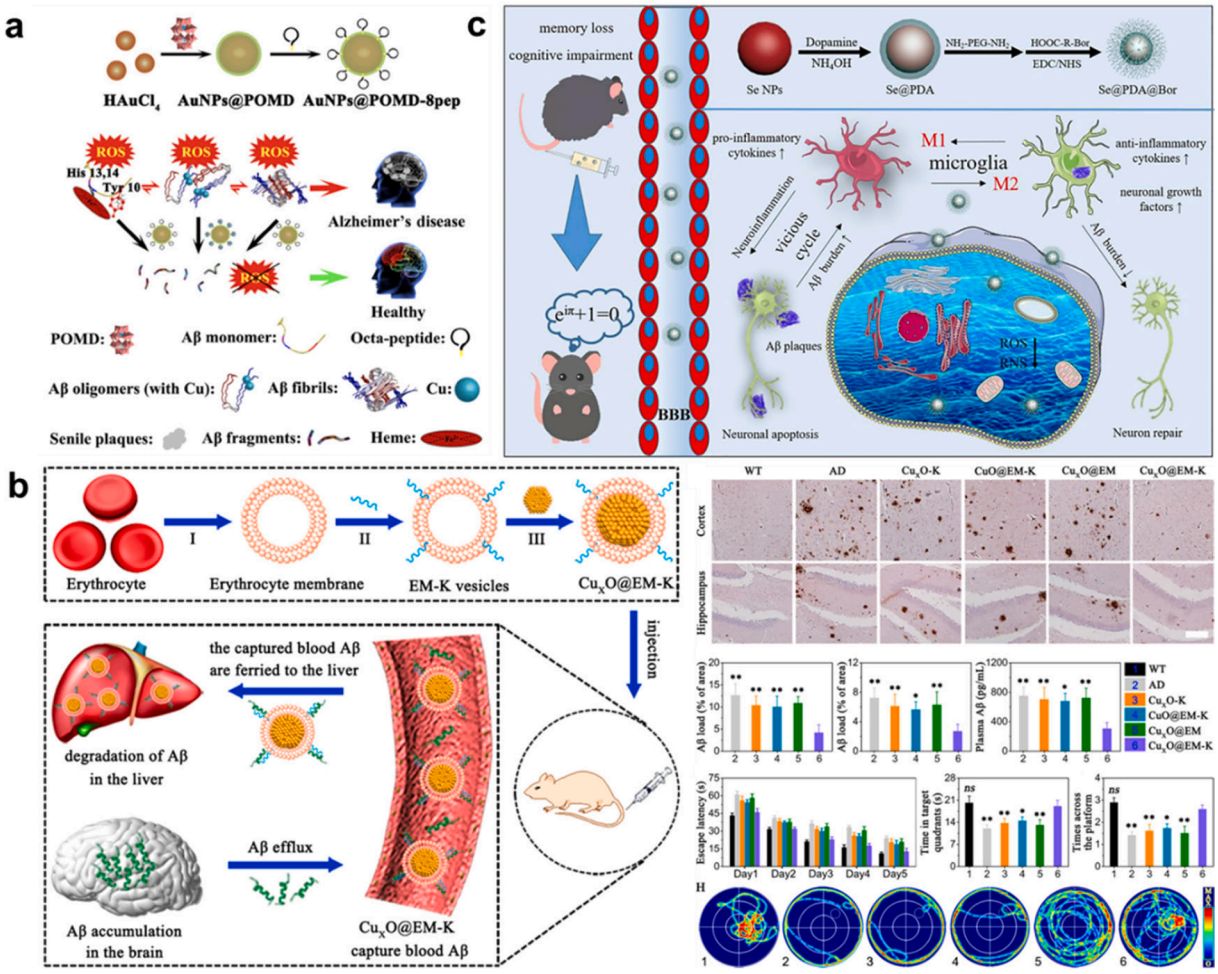

Fig. 10. Nanozymes for the treatment of AD. (a) Simultaneous consideration of multiple factors including Aβ, tau, and ROS. AuNPs@POMD-8pep exhibits dual functionality, being proficient in both depleting Aβ aggregates and scavenging ROS. (b) Targeted clearance of Aβ from peripheral organs. Cu_xO@EM-K efficiently captures Aβ present in the bloodstream, leading to a reduction in brain Aβ burden. (c) Ameliorating neuroinflammation. Se@PDA@Bor promotes the conversion of microglia from M1 to M2 by scavenging RONS, thus reducing neuroinflammation. Reprinted with permission from Refs. [175,176] and [178]. Copyright 2016 Springer Nature, 2020 American Chemical Society, and 2021 Elsevier.

and accumulated, which produces toxicity and promotes the gradual death of dopaminergic neurons, thereby causing dysfunction.[163] In addition to the abnormal accumulation of α-syn, the degeneration of DA neurons is heavily influenced by oxidative stress, which arises from an overproduction of ROS. Oxidative stress, in which mitochondrial dysfunction participates, leads to the accumulation of oxidized DA, ultimately leading to a decline in glucocerebrosidase activity and lysosomal dysfunction, causing neuronal degeneration.[164] As a pathogenic factor of prion-like spread, oxidative stress also leads to the inevitable spread of prion protein α-syn. [165] Additionally, oxidative stress can be mediated by neuroinflammation and microglia activation. In the inflammatory environment, arachidonic acid generates ROS under the action of lipid oxidase. Microglia can be activated by increased nitric oxide synthase-induced up-regulation of major histocompatibility complexes and glycoproteins, and expression of related inflammatory factors (tumor necrosis factor-α, interleukin-1β and -6) and molecules (adhesion molecules, cyclooxygenase-2, and $^{\bullet}NO$), which exacerbate the irreversible damage to DA neurons in SNc.[166]

As mentioned above, α-syn accumulation contributes to the progressive degeneration and eventual demise of DA neurons. Liu *et al.* found that the anti-oxidation nanozyme PtCu nano-alloys (NAs) significantly inhibited the diffusion of α-syn modeled by an intrastriatal injection of pre-made fibers. In addition, PtCu NAs significantly inhibited α-syn pathology, neurotoxicity, neuronal diffusion *in vitro*, and striatal to substantia nigra diffusion *in vivo* by scavenging ROS in primary neuron culture (Fig. 9a).[165] This study showed that antioxidant nanozymes may be used to combat the pathological diffusion of α-syn in PD. But unknown factors such as the biological safety of metal NPs in the brain, the permeability of BBB, and the long-term effect still need to be explored. Given the close association between PD and ROS, effective removal of ROS can protect tissues from OS, which contributes to the treatment of PD. The Cu_xO nanoparticle clusters (NCs) which exhibit analogical properties to CAT, GPx, and SOD studied by Hao *et al.* scavenged ROS and protected PD cells from neurotoxicity induced by oxidative stress. The nanozyme also showed good biocompatibility and therapeutic effect on 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD mice with oxidative stress-mediated neurological disorders.[167] This research may provide an opportunity for applying inorganic nanostructures with enzyme-like activity in biomedical and other bioengineering fields. ROS at different positions in cells plays different roles in diseases, so it is very necessary to develop cell-based localization nanozymes for ROS removal. To this end, Li *et al.* engineered lactoferrin-modified Au-Bi_2Se_3 nanodots located near the mitochondria, which significantly scavenge ROS in 1-methyl-4-phenylpyridinium$^+$ cells, thereby maintaining the normal mitochondrial membrane potential, and also showed a strong BBB penetration ability.[168] Ceria NPs designed and synthesized by Kwon *et al.* utilized regenerative redox switching between Ce^{3+} and Ce^{4+} ions to selectively

remove ROS. This study showed that the clearance of intracellular ROS through ceria NPs or the clearance of mitochondrial ROS through TPP conjugated-ceria NPs are able to effectively inhibit neuroinflammation and lipid peroxidation. Furthermore, this approach helped maintain the tyrosine hydroxylase (TH) level in the mouse striatum. However, the use of cluster-ceria NPs for the removal of extracellular ROS showed no therapeutic effect on maintaining TH level and inhibiting lipid peroxidation, which suggested reducing intracellular and mitochondrial rather than extracellular oxidative stress is essential for the treatment of PD (Fig. 9**b**). [169].

Neuroinflammation is also a detrimental factor in PD. Intraventricular administration of Prussian Blue nanozyme (PBzyme) in a PD mouse model can reduce DA degeneration and inhibit neuroinflammation. By scavenging ROS, PBzyme inhibited the activation of NLR family pyrin domain containing 3 (NLRP3) inflammasomes, down-regulating the cleavage of gasdermin D and the production of inflammatory factors, inhibiting microglia pyroptosis ultimately (Fig. 9**c**).[170] This study provided helpful insight into the mechanism of action and therapeutic strategies for treating PD through the use of pyroptosis inhibitors. Through adding an anti-inflammatory small molecule compound (quercetin), Li *et al.* made up for the shortcomings of inorganic nanozymes (Ptzyme) in alleviating the brain's inflammatory microenvironment.[171].

4.3.2. Alzheimer's disease

Nowadays, at least 50 million people worldwide suffer from AD, which is the most common among old people. Features of AD are the progressive decline of memory, cognitive, and behavioral functions. The brain of AD patients has moderate cortical atrophy, most notably of the multimodal limbic lobe structures and association cortices.[172] The accumulation of Aβ induces microglia polarization and activates toll-like receptors, leading to the release of multitudinous pro-inflammatory cytokines. Aβ overload also leads to the destruction of lysosomal degradation defects of Aβ fragment, triggering the release of cathepsin B, and prompting the assembly of NLRP3 inflammasome to amplify the inflammatory response.[173] In addition, tau that is involved in axonal transport of organelles is hyperphosphorylated and aggregated to form neurofibrillary tangles,[145] resulting in mitochondrial dysfunction and oxidative stress. Mitochondrial morphology is altered in the brain of AD subjects, with decreased activity of enzymes involved in oxidative phosphorylation.[174]

Since factors such as Aβ, tau, and ROS have intrinsic connections in the pathogenesis of AD, optimal therapeutic approaches necessitate simultaneous consideration of multiple factors. Gao *et al.* reported a reasonable design of nanozymes based on AuNPs. The aggregation of Aβ was impeded through the interaction between polyoxometalate (POM) featuring Wells-Dawson structure (POMD) and the cationic domain of His13 to Lys16. AuNPs easily grafted POMD onto its surface and also showed excellent ability in redox performance and BBB penetration. This nanozyme not only had protease-mimicking activity to consume Aβ aggregates, but also had SOD-mimicking activity to remove ROS, and exhibited potential for Cu removal as a metal chelator (Fig. 10**a**).[175] This study presented a compelling approach for the multifunctional treatment of AD by specifically modifying nanozymes. Guan *et al.* engineered a synthetic nanozyme, namely Ceria/Polymerases Hybrid (CeONP@POMs), which encompassed both proteolytic and SOD-mimicking activities. The findings showed that CeONP@POMs effectively hydrolyzed Aβ40 and reduced intracellular ROS. CeONP@POMs also crossed BBB, regulated microglia, and protected neurons from Aβ-related cytotoxicity *in vivo*.[31] Furthermore, recognizing the crucial involvement of peripheral organs in Aβ clearance within the brain, Ma *et al.* used Cu_xO nanozyme embedded into XTg-AD mouse erythrocyte membrane, incorporating the Aβ-targeted pentapeptide KLVFF3 to prepare Cu_xO@EM-K. The surface layer of the erythrocyte membrane can prevent the formation of protein corona, so as to retain its ability to target and clear Aβ in biological fluids and achieve the effect of rapidly reducing the Aβ level in the brain. The Cu_xO also had a variety of antioxidant enzyme-mimiking activities, which can effectively inhibit the oxidative damage of cell membrane induced by Aβ and stabilize the cell membrane (Fig. 10**b**).[176] This research innovatively transferred the action site of the nanozyme, presenting a valuable thought for improving the targeting of nanozymes. Due to tau hyperphosphorylation and tau aggregates playing an essential role in AD, Chen *et al.* rationally assembled mesoporous silica nanoparticles (MSN) with ceria and iron oxide nanocrystallines, and subsequently modified nanoassembly with Ga labeled Amino-T807 and loaded them with methylene blue MB to fabricate a hyperphosphorylated tau-targeted multifunctional nanocomposite. Ceria nanocrystals with SOD-like activity effectively eliminate excessive ROS, and thus inhibit tau hyperphosphorylation through alleviating the oxidative stress. At the same time, loaded MB can restrain the aggregation of hyperphosphorylated tau, thereby inhibiting neuronal apoptosis.[177]

Neuroinflammation assumes a significant part in the pathological process of AD as well. Gong *et al.* developed a Selenium-polydopamine nanozyme (Se@PDA@Bor) showing remarkable curative effect on AD. Studies have shown that the overproduction of pro-inflammatory cytokine fosters Aβ generation and additionally stimulates microglia proliferation and activation, resulting in a mutual cycle of Aβ aggregation and neuroinflammation. Se is an important component of selenoprotein systems, including glutathione and thioredoxin, which exhibit the capability to effectively scavenge ROS. Se@PDA@Bor exerted inhibitory effects on Aβ accumulation, preventing neuroinflammation reactivation, and breaking the vicious circle. Moreover, borneol (Bor) packaging made it easier to pass through BBB. Se@PDA@Bor restored its capacity to engulf Aβ and promote neuronal restoration by activating microglias from M1 to M2 phenotype. Experiments in APP/PS1 transgenic AD mice showed that nanozymes effectively regulated the neuroprotective capabilities of astrocytes and microglia within a brief timeframe. This intervention led to improvements in neuroinflammation, reduction of Aβ accumulation, as well as amelioration of memory decline and cognitive disorders (Fig. 10**c**).[178] Compared with the traditional single-target nanozyme, better targeting and biocompatibility can be achieved by the modified nanozyme. In this way, nanozymes offer notable advantages for treating AD.

4.3.3. Huntington's disease

HD is a dominant genetic disease which occurs on the autosome. Patients with HD initially exhibit changes in personality, mood, and mental status, sometimes accompanied by decreases in cognitive ability, followed by involuntary dance movements, bradykinesia, dystonia, stiffness, and dementia. Histone acetylation is widely recognized as a pivotal mechanism influencing cognitive functions. In HD, the aggregation of mutated huntingtin (HTT) proteins may decrease histone acetylation degree, resulting in neuronal damage and loss.[179] Oxidative stress also represents a significant contributor to the HD pathogenesis. Prolonged exposure to oxidative stress can damage DNA repair system, destroy cell structure, and cause mitochondrial dysfunction. The mutated HTT protein may inhibit the adaptive transcription process of oxidative stress.[180]

As mentioned, reducing intracellular aggregation of mutant HTT proteins would be a promising approach for treating HD. In the research carried out by Cong *et al.*, the efficacy of Se NPs in the treatment of HD based on the transgenic HA759 *C. elegans* HD model. 2 μM Se NPs significantly reduced ASH neuron death, axonal degeneration, and behavioral impairments. Furthermore, Se NPs provided protective effects against stress in *C. elegans*, thereby effectively restoring the normal response of *C. elegans* to external stimuli. As mentioned above, Se NPs that have strong antioxidant activity can reduce the ROS levels in HD nematodes. Its surface was easy to form protein coronas, which can inhibit the aggregation of HTT proteins in nematodes. In addition, down-regulating the expressions of histone deacetylase (HDAC)1, HDAC4, and sirtuin 1 can inhibit HD pathology in model organisms. The

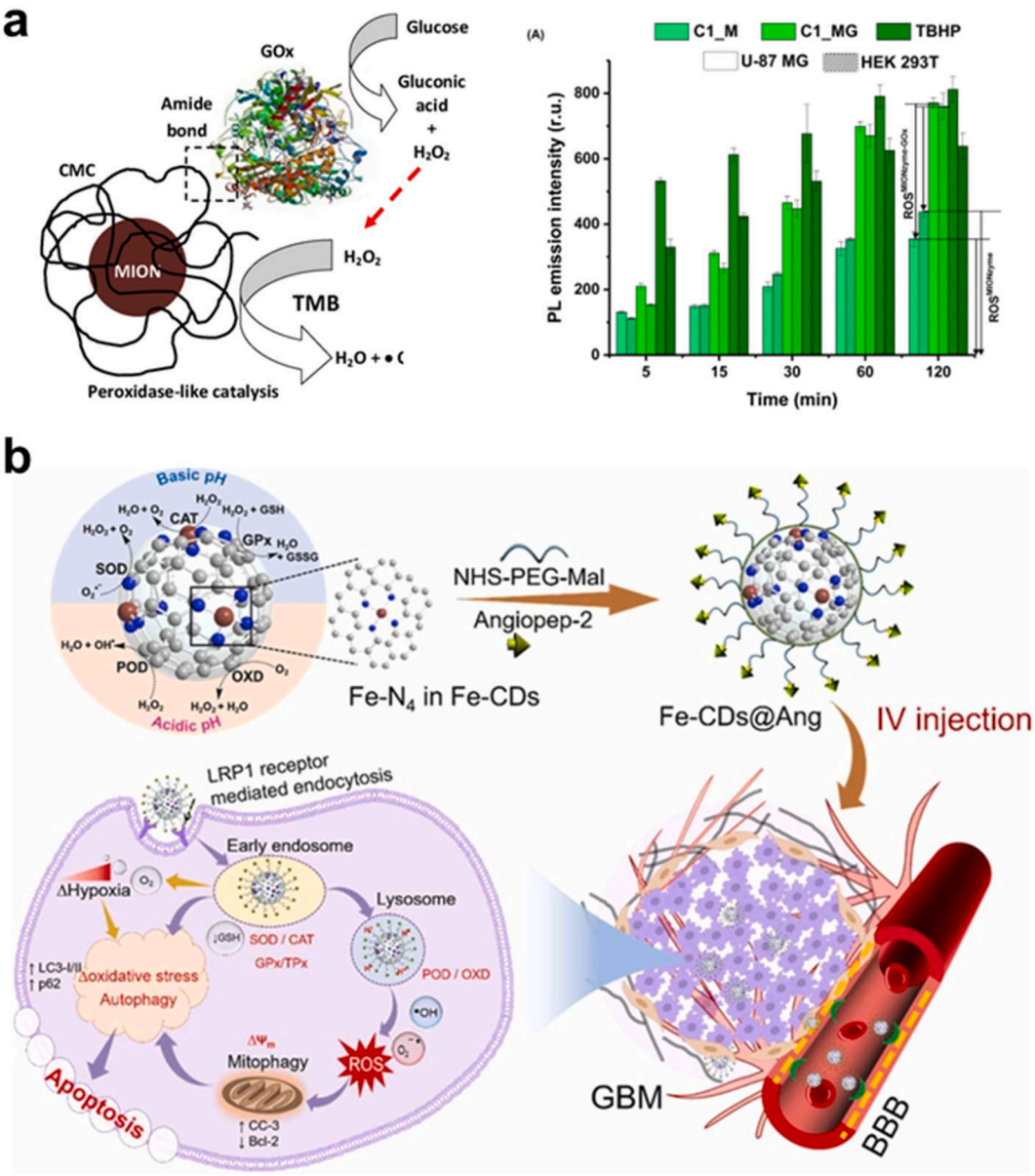

Fig. 11. Nanozymes for the treatment of brain cancer. (a) Hybrid nanostructure based on MIONzyme-GOx effectively mediates the accumulation of ROS by the cascade reactions of GOx enzyme and POD-like activity of nanozyme, and efficiently induces brain cancer cell death. (b) ROS-regulated enzyme-linked reaction induced by angiopep-2-functionalized Fe-CDs nanozymes to induce autophagy-lysosome pathway to treat GBM. Reprinted with permission from Refs. [187] and [29]. Copyright 2022 Elsevier.

mRNA levels of wild-type and HA759 nematodes treated with Se NPs were compared with those of the untreated group. After Se NPs treatment in HA759 nematodes, a significant decrease was observed in the expression levels of the associated genes including sir2.1, hda-1and hda-4. However, the mRNA levels of hda-2, 3, 6, 10 remained unchanged. [181] This study found that Se NPs protected and repaired neurological function under stress conditions, which may be conducive to the treatment of HD disease and has guiding significance for the rational design of Se NPs. However, since not all mRNA levels of HDAC members were decreased after treatment with Se NPs, we need to strengthen the epigenetic research on the effect of Se NPs on HDAC expression. This study also reminds us that the applied doses of other Se compounds should be considered when applying the nanodrug to treat HD, so as to ensure the safety of drug administration.

4.3.4. *Autosomal recessive spastic ataxia of Charlevoix-Saguenay*

ARSACS is an uncommon inherited neurodegenerative disorder that is primarily attributed to mutations in the *SACS* gene.[182] Sacsin encoded by the *SACS* gene is a protein on the surface of mitochondria, and its functional destruction makes the mitochondria show high perfusion balloon-like, thus impairing mitochondrial function. In the saccin-knockout mouse model, mitochondria are accumulated in the cell body and proximal dendrites of the saccin-knockout neurons, which may reduce mitochondrial transport to the dendrites, resulting in abnormal dendritic morphology and eventually neuronal cell death.[183] *SACS* mutations exacerbate oxidative stress and affect bioenergy metabolism. Consequently, this may amplify bioenergy deficits, establish a detrimental circle, and possibly promote cell death during neurodegenerative processes. Increased ROS production leads to mitochondrial bioenergy dysfunction, which is common in many neurodegenerative diseases. [184] Therefore, antioxidants have a great prospect in the treatment of ARSACS.

Polydopamine nanoparticles (PDNPs) contain abundant functional groups including imines and catechins, and they confer upon PDNPs the

capability to effectively clear substantial quantities of ROS. To evaluate the antioxidant properties of PDNPs, Battaglini *et al.* treated fibroblasts from healthy individuals and ARSACS patients with 100 μg/mL PDNPs. The results revealed that PDNPs significantly reduced basal ROS levels of these two types of cells, and were more potent than other antioxidant compounds, including nanostructured lipid carriers, tannic acid, and benzophenone. Apoptotic cells and necrotic cells increased significantly after treatment with 2.5 mM *tert*-butyl hydroperoxide solution (TBH), and decreased the number of living cells, while PDNPs treatment improved this situation. PDNPs also had a protective effect on mitochondria by recovering the mitochondrial elongation loss caused by TBH treatment. In the environment of 2.5 mM TBH and 6 mM oligomycin (a respiratory chain inhibitor), PDNPs played a role in preventing mitochondrial membrane potential loss. Furthermore, the PDNPs also showed good BBB permeability in the cross-porous BBB model which is established through the coculture of endotheliocytes and astrocytes. [185] This study demonstrated the outstanding antioxidant and mitochondrial protection capabilities of PDNPs, providing a promising basis for the utilization of PDNPs as a prospective therapeutic approach to ARSACS. However, further studies *in vivo* are needed to analyze the signaling pathways affected by PDNPs, which would be imperative for advancing the clinical applications of PDNPs.

4.4. Other diseases

4.4.1. Brain cancer

Brain cancer is widely recognized as one of the most lethal diseases affecting the nervous system. Among brain cancers, glioblastoma multiforme (GBM) continues to prevail as the most prevalent and deadly form. In addition, brain metastases are the most common neurological complication of systemic cancers, with a significantly higher prevalence than primary brain tumors. Traditional cancer treatments, including surgical resection, radiotherapy, and chemotherapy, have shown the disadvantages, such as poor prognosis.[186] However, the intracellular pathways and metabolic patterns of tumor cells are quite different from those of healthy cells, including local high concentration of H_2O_2, hypoxia, uneven blood perfusion, and extracellular acidic pH caused by glycolytic metabolism of cancer cells, etc., which offer a multitude of prospects for developing prospective anticancer therapies and minimize the adverse reactions on healthy cells.[187] It is noteworthy that in addition to antioxidant nanozymes mitigating the development of most brain diseases by consuming excessive RONS, pro-oxidative nanozymes with OXD and POD-like activities also hold significant therapeutic value, particularly in brain tumor therapy.[188]

On the one hand, chemodynamic therapy (CDT) mediated by POD-like active nanozymes converts endogenous H_2O_2 into highly harmful $^{\bullet}OH$ through Fenton or Fenton-like reactions, thus capable of directly inducing massive cell death. However, in the TME, the concentration of H_2O_2 is insufficient to sustain $^{\bullet}OH$ production.[189] Therefore, enhancing the local concentration of H_2O_2 within TME is needed to accelerate the Fenton or Fenton-like reactions, thereby improving the efficacy of CDT. Mansur *et al.* designed and fabricated a hybrid nanostructure composed of superparamagnetic iron oxide. This innovative nanostructure was subjected to functionalization and stabilization using carboxymethyl cellulose biopolymer. Additionally, it underwent a covalent bioconjugation process with GOx, resulting in the formation of MIONzyme-GOx. MIONzyme-GOx consumed glucose nutrients through GOx-catalyzed biological reaction and generated $^{\bullet}OH$ through H_2O_2 catalyzed by a Fenton-like reaction under the acidic pH of TME, leading to cell death. Compared with "pure" MIONzyme, MIONzyme-GOx had higher toxicity to glioblastoma cells (Fig. 11**a**).[187]Besides, Mansur *et al.* synthesized Au NPs stabilized by trisodium citrate (AuNPs@TSC) to mimic OXD. Additionally, they coupled cobalt-doped superparamagnetic iron oxide NPs stabilized by carboxymethylcellulose ligands (Co-MION@CMC) to mimic POD. Here, TSC mimicked GOx, catalyzing the production of H_2O_2 to accelerate the Fenton reaction. Co^{2+} contributed to an elevation in the magnetocrystalline anisotropy. Co-MION@CMC can improve the thermal therapy performance of magnetite NPs, which can also be used for magnetic thermal therapy. The nanosystem was connected with an iRGD sequence (9-amino acid cyclic peptide, sequence: CRGDKGPDC) as a targeting peptide to recognize αvβ3 integrin which is often overexpressed in brain tumor cell membranes to positively target GBM cancer cells.[190] In this study, the double inorganic nanozymes system was used to compensate for the instability of natural enzymes, which induced biocatalytic cascade reactions in TME, and achieved the combined magnetothermal-chemical therapy, providing an effective strategy for the design of hybrid nanozyme systems. However, further studies *in vivo* are necessary to design the features of nano-systems to improve the biodistribution and clearance/excretion of nano-preparations, making nanozymes beneficial for the clinical treatment of cancer.

On the other hand, apart from stand-alone applications, nanozymes can also improve TME, enabling their synergistic application alongside other treatment methods such as chemotherapy, radiotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), sonodynamic therapy, and immunotherapy. This combination serves to enhance therapeutic efficacy while mitigating adverse reactions. For example, malignant GBM cells that are resistant to chemotherapy exhibit increased vulnerability to autophagic cell death pathways.[191] The CDs synthesized by Muhammad *et al.* supported iron monatomic nanozyme (Fe-CDs) to show multiple enzyme activities of OXD, POD, CAT, SOD, GPx, and thiol peroxidase (TPx). To effectively target low-density lipoprotein receptor–related protein-1, which is highly expressed in brain capillary ECs and tumor cells, the Fe-CDs underwent chemical modification by Angiopep-2 (Fe-CDs@Ang). Fe-CDs@Ang which exhibited inherent OXD/POD-like activity accumulated within the acidic *endo*-lysosomes (pH 4–5), impairing lysosomal degradation capacity and inducing autophagy, thereby overcoming drug resistance in solid GBM. Furthermore, SOD, CAT, and GPx-like activities can enhance autophagy and lysosome-based apoptosis, and alleviate hypoxia (Fig. 11**b**).[29] Yin *et al.* developed a Gd_2O_3@Ir/TMB-RVG29 (G@IT-R) nanomachine that can achieve tumor-specific PTT. Under the activation of acidic TMB and high concentration of H_2O_2, Ir nanozyme exhibited POD-like activity, enhancing the color reaction of the photothermal agent TMB, ultimately enabling tumor-specific PTT.[27] In addition to the above-mentioned nanozymes synergizing a single therapy, synergizing two or more complex therapeutic systems is also a current research trend. Sunil *et al.* reported nanozymes (BIONs) with photodynamic and immunological activities. The CeO_2 nanozyme exhibited a pro-oxidative effect in tumor sites to enhance the efficacy of PDT, while exerting an antioxidant effect in healthy tissues like the kidneys.[192]

4.4.2. Cerebral malaria

Malaria is a parasitic disorder resulting from malaria parasites transmitted by mosquitoes, among which *P. falciparum* can cause CM, a life-threatening neurological complication. The parasitized red blood cell expresses *Plasmodium falciparum* erythrocyte membrane protein-1 on the surface, enabling its interaction with membrane proteins of ECs including intercellular adhesion molecule-1. ECs phagocytize merozoites and presents malaria antigen to $CD8^+$ T cells. This interaction will trigger BBB destruction mediated by interferon-γ and perforin,[193] causing fluid and protein to leak from the circulatory system to the intercellular matrix, thereby forming angioedema.[194] A research report of live mice utilizing whole brain covered high-field MRI showed that inflammatory destruction and vasogenic edema of the BBB began with the olfactory bulb and then spread deep into the brain along a distinct pathway known as the rostral migratory flow. Ultimately, this pathological process extended toward the brain stem, leading to coma and death.[195] The release of free heme from parasitized red blood cells (RBCs) may generate excessive ROS and damage ECs and BBB. [196]

Plasmodium infection may eventually result in the inflammatory

Table 4
A summary of nanozymes for brain disease treatment.

Brain Diseases	Nanozymes	Activities	Mechanisms	References
Ischemic Stroke	HPBZs	CAT, POD, SOD	ROS scavenging, inhibition of apoptosis, anti-inflammatory	[138]
	CeO_2	CAT, SOD	ROS scavenging, inhibition of apoptosis	[146]
	EA/P-CeO_2	CAT, SOD	ROS scavenging, BBB protection	[147]
	CeO_2 @ZIF-8 NPs	CAT, POD	ROS scavenging, inhibiting lipid peroxidation, reducing the oxidative damage and death of neurons, anti-inflammatory	[148]
	PEG-Fe_3O_4	CAT, POD, SOD	ROS scavenging, facilitating BBB reconstruction	[150]
	MeNPs	SOD	multi-antioxidative, anti-inflammatory	[151]
	Eda-MnO_2 @Tf	CAT, SOD	ROS scavenging, anti-inflammatory	[30]
	Co-Fe_3O_4	CAT, POD	RONS scavenging	[153]
	MPBzyme @NCM	CAT, SOD	ROS scavenging, enhanced differentiation of microglia polarization from M1 to M2, reducing recruitment of neutrophils, inhibition of neuronal apoptosis, increasing the proliferation of neurocytes	[152]
	Carbon dot	SOD	intracellular excess ROS scavenging	[53]
	PNzyme/MnO_2	CAT, SOD	thrombolysis multilevel, precise targeting, ROS scavenging, anti-inflammatory	[154]
Traumatic Brain Injury	O-NZ	SOD, GPx	RONS scavenging, improving neurocognition and memory by up-regulation of heme oxygenase-1	[158]
	Carbogenic nanozyme	CAT	ROS scavenging, immune suppression	[157]
	TriM nanozyme	CAT, POD	RONS scavenging	[161]
	Pt/CeO_2	CAT, GPx, POD, SOD	RONS scavenging, anti-neuroinflammation	[159]
	Cr/CeO_2	CAT, GPx, SOD	RONS scavenging, anti-neuroinflammation	[160]
Parkinson's Disease	PtCu NAs	POD, CAT, SOD	inhibiting α-syn pathology and spreading, reducing cell apoptosis and interneuronal transmission	[165]
	Cu_xO NCs	CAT, GPx, SOD	ROS scavenging	[167]
	Lf-Au-Bi_2Se_3 NDs	POD, SOD, CAT, GPx	protecting the mitochondria from oxidative stress, improvement of behavioral performance and neuronal damage	[168]
	Ceria/TPP-Ceria NPs	SOD, CAT	intracellular or mitochondrial ROS scavenging, inhibition of neuroinflammation and lipid peroxidation	[169]
	PBzyme	CAT, POD, SOD	reducing dopamine degeneration, anti-neuroinflammation	[170]
	Que/Ptzyme@Man-PLGA	SOD, CAT	ROS scavenging, anti-neuroinflammation, promoting microglial polarization toward an anti-inflammatory M2 phenotype	[171]
Alzheimer's Disease	AuNPs@POMD-8pep	Protease, SOD	Aβ aggregates depleting, Aβ-mediated ROS scavenging, removing Cu from Cu-induced Aβ oligomers	[175]
	CeONP@POMs	Protease, SOD	Aβ aggregates depleting, intracellular ROS scavenging	[31]
	Cu_xO@EM-K	CAT, SOD, GPx	peripheral Aβ aggregates depleting	[176]
	CeNC/IONC/MSN-T807-MB	SOD	ROS scavenging, inhibition of tau hyperphosphorylation and aggregation	[177]
	Se@PDA@Bor	SOD, CAT	RONS scavenging, restoration of mitochondrial homeostasis	[178]
Huntington's Disease	Se nanoparticles		ROS scavenging, suppression of proteins aggregation, down-regulating mRNA levels of HDAC family members	[181]
ARSACS	PDNPs		recovering the mitochondrial elongation loss, intracellular ROS scavenging	[187]
Brain Cancer	MIONzyme-GOx	POD, GOx	direct destruction of brain cancer cells	[191]
	AuNP@TSC-Co-MION@CMC	OXD, POD	direct destruction of brain cancer cells	[193]
	Fe-CDs@Ang	POD, OXD, SOD, CAT, TPx GPx	regressing the GME tumor, overcoming the drug resistance	[194]
	Gd_2O_3@Ir/TMB-RVG29	POD	tumor specific PTT	[27]
	BIONs		enhancing PDT curative effect, initiation of adaptive immune response	[192]
Cerebral Malaria	Fenozyme	CAT, POD	ROS scavenging, anti-inflammatory	[18]
Major Depression Disorder	CeO_2@BSA	CAT, SOD	ROS scavenging, improvement of depression-like behaviors, anti-neuroinflammation	[200]

destruction of BBB, and the excessive ROS. Therefore, the treatment of CM by improving BBB damage and eliminating ROS has a significant effect. Zhao *et al.* developed a novel type of ferritin nanozyme (Fenozyme), which was constructed from recombinant human ferritin (HFn) shell that selectively targeted the BBB ECs, and the internal Fe_3O_4 nanozyme core that had CAT-like activity to achieve ROS clearance. The results showed that Fenozyme significantly increased the activity score of experimental cerebral malaria (ECM) mice. By combining HFn receptors, Fenozyme was targeted to BBB ECs, therefore protecting the BBB barrier's integrity by scavenging ROS. Treatment with Fenozyme or HFn protein can reduce the RBCs percentage infected by parasites. Moreover, Fenozyme and HFn resulted in a substantial elevation in the population of macrophages within the liver of ECM mice, notably stimulated the proliferation of macrophage Raw264.7, and enhanced the phagocytosis of bone marrow-derived macrophages to $pRBCs^{GFP}$ and $nRBCs^{GFP}$. This result showed that Fenozyme alleviated parasitemia by enhancing the proliferation and phagocytosis of macrophages. In addition, Fenozyme also effectively alleviated neurological sequelae in ECM mice treated with artemether.[25] This study has provided a strong theoretical basis for strengthening the targeting of nanozyme therapy and its joint application with other drugs, as well as valuable ideas for studying how to treat the injuries of other tissues in CM.

4.4.3. Depression disorder

Depression disorder is an emotional dysfunction caused by genetic system abnormalities or acquired environmental changes. Although current treatment options encompass medication, psychotherapy, and physical therapy, their efficacy remains constrained. The pathology of depression disorder is complex and diverse, involving genetic and psychosocial stress, stress hormones and cytokines, monoamine synthesis, glutamate, and aminobutyric acid neurotransmission.[197] Studies have shown that excessive ROS accumulation stands out as a prominent

factor contributing to the pathological characteristics of depression.[18] In the depressed state, the imbalance of redox homeostasis of cells aggravates the depressive behavior, reduces the ability of neurogenesis in the hippocampus, increases the loss of astrocytes, and leads to brain dysfunction and abnormal signal transmission process of neurons.[198] $O_2^{\bullet-}$ in the mouse brain peroxisome increases during oxidative stress, leading to the inactivation of CAT. This inactivation results in elevated intracellular H_2O_2 levels increases and tryptophan hydroxylase-2 (TPH2) is further oxidized. A decrease in that level of TPH2 leads to dysfunction of the 5-hydroxytryptamine system in the brain, ultimately contributing to depression disorder.[199]

Fu *et al.* employed the bovine serum albumin (BSA) culture method to synthesize a new antidepressant nanodrug CeO_2@BSA, which showed significant scavenging ability to $O_2^{\bullet-}$ and $^{\bullet}OH$ at 0.025 μg/mL and 2.5 μg/mL Ce concentration respectively, and significantly reduced the proportion of ROS^+ cells. In contrast to the group treated with PBS, the administration of CeO_2@BSA nanocluster to mice led to a significant reduction in ROS levels of the mouse brain. CeO_2@BSA therapy restrained the increase of $IBA1^+$ activated microglia induced by chronic restraint stress, saved the down-regulation of a brain-derived neurotrophic factor, and reversed the down-regulation of protein synaptophysin and PSD95, which indicated that CeO_2@BSA had anti-inflammatory and neuroprotective effects in depression.[200] This study proved that CeO_2@BSA could effectively modulate pathological changes and ameliorate depression-like behaviors, confirming ROS as a therapeutic target for depression and offering inspiration for future research.

5. Challenges and perspectives

Oxidative balance is key for maintaining homeostasis. Excessive ROS will attack biomacromolecules directly and disturb normal signaling pathways, resulting in severe brain diseases. Nanozymes, as a new antioxidant, show great potential in regulating oxidation pressure (Table 4). As a new star, nanozymes have been concerned widely and developed rapidly, but also faced with general problems and challenges that need to be solved.

(1) Comprehension and regulation of the *in vivo* biological behavior of nanozymes. Nanozymes have shown good catalytic activity *in vitro*, but their distribution, activity, and metabolism *in vivo* still need further in-depth investigation. Thus, a more systematic and comprehensive bioeffect of nanozymes is essential to translational applications.

(2) Design and development of novel catalytic types of nanozymes. There are seven types of natural enzymes, which are oxidoreductase, transferases, hydrolases, lyases, isomerases, ligases, and translocases. Among these, oxidoreductases, hydrolases, lyases, and isomerases have been realized in nanozymes, and there are still transferases and ligases cannot do. So, developing novel catalytic types of nanozymes and multienzyme mimetic activity of nanozymes represent a crucial direction. This is especially relevant for brain diseases, which often involve complex biochemical processes.

(3) Deciphering the catalytic mechanism of nanozymes, and achieving activity controllability *in vivo*. Different brain diseases may require different catalytic reactions, and these are quite complicated. But the universal conclusions or rules of nanozymes are few. The exploration of catalytic mechanism serves as a guiding force for the rational design as well as activity controllability of nanozymes with desired. The physicochemical properties of nanozymes, encompassing constituent atoms, crystal forms, sizes, and surface modifications, can be customized to optimize their catalytic activity, making them more suitable for diagnosing and treating particular brain diseases.

(4) Expanding the application scenarios of nanozymes. The versatile attributes of nanozymes, including superparamagnetism, fluorescence, photothermal capabilities, BBB penetration, and enzymatic activity, coupled with their facile functionalization, position them as highly promising tools in the realm of theranostic applications in brain diseases. The further promotion of nanozymes depends on the matched biomedical application scenario. How to combine different characteristics of nanozymes with brain diseases, making the best use of advantages and bypassing the disadvantages will promote the nanozymes from bench to bedside.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgements

This work was financially supported by CAS Interdisciplinary Innovation Team (JCTD-2020-08), National Natural Science Foundation of China (No. 82122037) and Youth Innovation Promotion Association of Chinese Academy of Sciences (2019093).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccr.2023.215519.

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