Metal ions are heavily involved in the membrane potential and intracellular activities of cells. Increasing evidences have shown that it is critical to evaluate the ion levels and monitor their dynamic changes in the brain for the diagnosis of neurodegenerative diseases (NDDs), including Alzheimer’s disease, Parkinson’s disease, Huntington disease, amyotrophic lateral sclerosis, and so on. Herein, the roles of metal ions in the occurrence and development of NDDs are intensively discussed, and the recent advances in probes and sensors for ion-level detection are summarized. Finally, the further applications of ingenious ion-selective probes and sensors are outlined, highlighting the future opportunities for the metal ion-based diagnosis of NDDs.

1. Introduction

In human, elements such as hydrogen (H), carbon (C), nitrogen (N), and oxygen (O) are organic and bulk, while sodium (Na), potassium (K), magnesium (Mg), calcium (Ca), chlorine (Cl), phosphorus (P), and sulfur (S) are the seven macrominerals.[1] Also, there are trace elements, including iron (Fe), copper (Cu), zinc (Zn), and manganese (Mn). Although the definite functions of these elements require further investigation, some of them, particularly those metal ions, are proved to be critical in biological systems.[2] These ions can be categorized into the following groups based on their biological functions: 1) ions, e.g., K ions (K⁺), Na ions (Na⁺), H ions (H⁺), and Cl ions (Cl⁻), involved in cellular membrane potential; 2) ions, e.g., Fe ions (Fe²⁺/³⁺), Cu ions (Cu¹⁺/²⁺), Mn ions (Mn²⁺/³⁺), Zn ions (Zn²⁺), and Ca ions (Ca²⁺), involved in intracellular activities. The impaired ion homeostasis leads to abnormal physiological activities of the body, and consequently triggers the occurrence and development of various diseases.[3] Particularly, ion dyshomeostasis has been demonstrated to be closely associated with neurodegenerative diseases (NDDs),[4] including Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington disease (HD), amyotrophic lateral sclerosis (ALS), and so on.

Recently, several approaches for ion-level detection have been developed and applied in vitro and in vivo,[5] which provide a promising avenue to the diagnosis of NDDs. In this perspective, we summarize the representative advancements bridging the ion levels and NDDs, and highlight the recent advances of ion-selective probes and sensors applied to NDDs. Finally, promising insights for further preclinical and clinical research will be outlined, which will make important breakthroughs for telltale signs of NDDs.

2. Ion Dyshomeostasis in NDDs

Ion dyshomeostasis is involved in a series of pathophysiological processes that are tightly associated with NDDs, including abnormal membrane potential and disordered intracellular activities (e.g., pathological protein generation, oxidative stress, organelle dysfunction, and enzymatic activity disorder). In this section, the correlation between ion dyshomeostasis and pathological changes in various NDDs is reviewed to highlight the key roles of ions in the development of NDDs (Figure 1).

2.1. Ions Related to the Membrane Potential in NDDs

K⁺, H⁺, Na⁺, and Cl⁻ can traverse across the corresponding ion channels on cytomembrane to regulate the cell excitability and
the release of neurotransmitters via adjusting the resting membrane potential and action potential.\textsuperscript{[6]} For example, ATP-sensitive K\textsuperscript{+} channels are involved in controlling resting membrane potential due to the K\textsuperscript{+} efflux,\textsuperscript{[7]} while selective permeation of K\textsuperscript{+} via voltage-dependent K\textsuperscript{+} (K\textsubscript{v}) channels can efficiently modulate the shape and frequency of action potential, and repolarization in the neurons.\textsuperscript{[8]} In addition, H\textsuperscript{+}-associated proton pumps are closely related to the mitochondrial membrane potential, which is essential for the energy storage and the generation of ATP.\textsuperscript{[9]} Likewise, the transmembrane transport of Na\textsuperscript{+} through Na\textsuperscript{+} channels leads to the generation of action potentials.\textsuperscript{[10]} Moreover, Cl\textsuperscript{-}/C0\textsuperscript{-} plays a key role in maintaining the resting membrane potential, which depends on extruding intracellular Cl\textsuperscript{-} and K\textsuperscript{+} via potassium–chloride cotransporter 2 under normal conditions.\textsuperscript{[11]} The dyshomeostasis of these ions leads to the abnormal membrane potential, which affects neurophysiological function and stimulates conduction, thus causes various diseases, such as epilepsy, which is induced by abnormal K\textsuperscript{+} levels via K\textsubscript{v} channels.\textsuperscript{[12]} In addition, researchers have demonstrated the increased Na\textsuperscript{+} level and the decreased K\textsuperscript{+} level in cingulate gyrus of AD patients than that of the healthy controls,\textsuperscript{[13]} again signifying the importance of ion levels. Consequently, K\textsuperscript{+}, H\textsuperscript{+}, Na\textsuperscript{+}, and Cl\textsuperscript{-} play significant roles in abnormal neuronal activities in lesions of NDDs.

2.2. Ions Related to the Intracellular Activities in NDDs

The abnormal levels of Fe\textsuperscript{2+/3+}, Cu\textsuperscript{1+/2+}, Mn\textsuperscript{2+/3+}, Zn\textsuperscript{2+}, and Ca\textsuperscript{2+} contribute to the intracellular pathological changes in NDDs,\textsuperscript{[14]} including the generation of pathological proteins, oxidative stress, organelle dysfunction, enzymatic activity disorder, and so on. In this section, the abnormal intracellular activities induced by ion dyshomeostasis are introduced.

2.2.1. Ions Related to Pathological Protein Generation

Cu\textsuperscript{1+/2+} is essential for many physiological processes of the brain, such as energy and ion metabolism, angiogenesis, antioxidative defense, and so on.\textsuperscript{[15]} Recently, a high level of Cu\textsuperscript{1+/2+} was observed in the amyloid plaques of the AD patient’s brain.\textsuperscript{[16]} Excessive Cu\textsuperscript{2+} binds with the thiol or amino groups of amyloid-beta (A\textsubscript{B}) peptides and leads to the coordination of intramolecular bridges between A\textsubscript{B} peptides, thus accelerating the aggregation of A\textsubscript{B} peptides.\textsuperscript{[15,17]} Moreover, Cu\textsuperscript{2+} is reduced to Cu\textsuperscript{+} by the hydroxyl radicals initiated in the process of A\textsubscript{B} plaques generation.\textsuperscript{[16,18]} Similarly, the level of Zn\textsuperscript{2+} is observed to be two- to threefold higher in the A\textsubscript{B} of AD patient’s brain than that of the healthy control.\textsuperscript{[19]} Moreover, previous studies have demonstrated that the imbalance of Cu\textsuperscript{2+} could damage the dopaminergic neurons accompanied by the abnormal aggregation of \(\alpha\)-synuclein,\textsuperscript{[20]} which is a key clue to the lesions in PD.

2.2.2. Ions Related to Oxidative Stress

Fe\textsuperscript{2+/3+} is an essential metal ion involved in multiple cellular functions, including energy production, myelination, synaptic activity, and other basic cellular processes.\textsuperscript{[21]} Under normal condition, Fe\textsuperscript{3+} is nontoxic at the normal level,\textsuperscript{[22]} and capable of maintaining homeostasis via ferritin, thus playing a key role in iron storage. However, inflammation, a common pathological change in NDDs, can damage ferritin and cause excess iron accumulation and labile iron pools in neurons, inducing cell death.\textsuperscript{[23]} It is proved that the accumulated iron can progressively migrate to the cytosol, increasing the reactive oxygen species level and aggravating the inflammation concurrently.\textsuperscript{[16]} Moreover, the high level of Cu\textsuperscript{2+} in the brain of HD patients promotes cellular...
damage and leads to neuronal death,[24] due to the reduction of Cu²⁺ to Cu⁺.[25]

2.2.3. Ions Related to Organelle Dysfunction

The decreased matrix calcium in AD patients provokes a compensatory increase in intracellular calcium level, leading to the mitochondrial dysfunction and physiopathologic changes in the brain of AD patients.[26] Moreover, Ca²⁺ dyshomeostasis is associated with the organelle dysfunction in ALS. The endoplasmic reticulum (ER), lysosome, and mitochondria are the Ca²⁺-storing organelles in cells, consequently the Ca²⁺ dyshomeostasis may affect mitochondrial dynamics and ER/lysosomal function, triggering motor neuron demise in ALS.[27]

2.2.4. Ions Related to Enzymatic Activity Disorder

Cu²⁺/Zn²⁺ is one of the basic components and it constitutes multiple essentialities, which are involved in the physiological processes for the maintenance of cell functions.[28] For example, Cu²⁺ mainly serves as a cofactor at the active sites of essential enzymes, such as cytochrome c oxidase.[28,29] The binding of Cu²⁺ with thiol, amino, or sulfhydryl groups of enzymes could inhibit the activities of cytochrome P450 oxidative system, GSH transferases, lactate dehydrogenase, Na⁺/K⁺-ATPase, and so on.[15,30] Moreover, the excess Zn²⁺ can reduce the activity of protein tyrosine phosphatases, which is an important dephosphorylation enzyme that plays a key role in reducing the hyperphosphorylation of tau.[11] Similarly, Mn²⁺/Zn²⁺ is related to the metabolism of lipids and proteins as a key cofactor in numerous kinases and enzymes, especially the Mn-dependent enzymes (e.g., arginase, agmatinase, glutamine synthetase, and so on).[12] Consequently, the involvements of ions in activities of multiple enzymes are likely to be intertwined. Once these ion levels become out-of-balance, the activities of multiple enzymes could be influenced, further triggering the complex pathology of NDDs.

3. Ion-Level Detection

As each ion plays vital roles in physiological and pathological processes, the efficient methods for sensitive and selective detection of ion levels are urgently demanded. To date, various methods have been developed for ex situ and in situ ion-level detection, contributing to the diagnosis of NDDs.

3.1. Ex situ Analysis

To efficiently analyze the ion levels of brain tissues, the ex situ qualitative and quantitative analysis methods have been developed, including inductively coupled plasma mass spectrometry, Raman scattering spectroscopy, X-ray fluorescence spectrometry, and so on.[13] For example, K⁺ can react with sodium cobaltinitrite to form potassium–sodium cobaltinitrite that can be selectively detected via Raman scattering,[14] providing an effective approach in detecting K⁺ level in cerebrospinal fluid. Moreover, photoelectrochemical has been recognized as a promising approach to detect metal ions with high sensitivity.[15] However, the samples detected by the aforementioned methods are mainly isolated tissues, which is difficult to reflect the dynamic changes in ions in vivo.

3.2. In situ Analysis

Recently, several ion-level detection methods have been developed for in situ analysis, including small-molecule fluorescent probes and nanosensors. The ingenious design of ion-selective probes and sensors is highly valuable in monitoring dynamic changes in ions in vitro and in vivo.

3.2.1. Small-Molecule Fluorescent Probes for In Situ Analysis

Small-molecule fluorescent probes, mainly based on the organic dye, have been developed rapidly with success in in situ ion-level detection. Recently, ratiometric fluorescent probes have been designed and synthesized for the detection of various metal ions, including Na⁺, Fe²⁺/³⁺, Cu²⁺, and Zn²⁺ (Table 1). For example, a small-molecule probe, NaGY-AM, exhibits fluorescence emission peaks at 565 and 620 nm in the absence and presence of Na⁺, respectively (Figure 2a), which realizes the visualization of exogenous Na⁺ in HeLa cells.[36] There are also small-molecule fluorescent chemosensors for K⁺ detection in cytoplasm and mitochondria.[37] The increasing number of studies have shown that fluorescent probes based on fluorescence resonance energy transfer (FRET) play a key role in ion detection. Chang and co-workers developed a FRET-based probe FIP-1 for Fe²⁺ detection in MDA-MB-213 cells. The FRET effect occurs between the fluorescein and Cy3 depending on an endoperoxide bridge in the absence of Fe²⁺, while the effect is disrupted by the cleavage of the endoperoxide bridge induced by Fe²⁺ (Figure 2b).[36] The Fe²⁺ probe, NAP-3, shows an obvious decrease in emission signal intensity at 544 nm in the absence of Fe²⁺ while a sharp increase at 605 nm after binding with Fe³⁺.[39] For Cu²⁺ detection, TY-1 and TY-2, two FRET-based fluorescent probes, have been designed, which could detect Cu²⁺ both in HeLa cells and glioma cells.[40] In addition, an ingenious fluorescent probe, S1, has been developed to detect Cu²⁺ in live MCF-7 cells (Figure 2c).[41,42] Notably, there was no fluorescence signal observed in mice subcutaneously injected with probe S1, while the fluorescence signal across the fur of mice was enhanced remarkably by subsequent subcutaneous injections of excessive Cu²⁺. Moreover, it is proved that S1 could cross the blood–brain barrier (BBB) to enter the brain via high-performance liquid chromatography experiment of probe S1 and brain tissue, showing a potential ability to detect Cu²⁺ in NDDs. Recently, a copper-directed acyl imidazole probe has been constructed and applied to monitor labile copper pools in neurons, astrocytes, and microglia, thereby contributing to the understanding of metal metabolism in cells.[43] For Zn²⁺ detection, there is a two-photon fluorescent probe Chromis-1, the emission peak of which changes from 440 to 510 nm under the influence of Zn²⁺ in NIH3T3 fibroblasts.[44] Moreover, a two-photon fluorescence probe, P-Zn, has been developed for monitoring Zn²⁺ in live cell, hippocampal tissue, and zebrafish (Figure 2d).[42,43] In the presence of Zn²⁺, the initial emission peak at 465 nm decreased...
Table 1. Overview of the reaction groups, mechanisms, and applications of representative probes.

| Detected ions | Structures of fluorescent probes (functional groups illustrated by the red boxes) | Mechanisms | Detection limit | Applications | Ref. |
|---------------|---------------------------------------------------------------------------------|------------|----------------|--------------|-----|
| Na⁺           | ![Na⁺ Probe](image1)                                                            | D–π–A systems | 5 mM           | HeLa cells   | –   | [36]|
| Fe²⁺          | ![Fe²⁺ Probe](image2)                                                           | FRET       | 10 μM          | MDA-MB-213 cells | – | [38]|
| Fe³⁺          | ![Fe³⁺ Probe](image3)                                                           | D–π–A systems | 9.1 nM         | HepG2 cells  | C. elegans | [39]|
| Cu²⁺          | ![Cu²⁺ Probe](image4)                                                           | FRET       | 42 nM          | HeLa cells and glioma cells | – | [40]|
|               | ![Cu²⁺ Probe](image5)                                                           | FRET       | 9.1 nM          | HeLa cells and glioma cells | – | [40]|
|               | ![Spirocyclic on-off](image6)                                                   |            | 1.95 nM        | MCF7 cells    | Mice | [41]|
|               | ![Spirocyclic on-off](image7)                                                   |            | Copper-mediated activation of acyl imidazole | HEK293T cells, primary neurons, human astrocytes and microglia | – | [43]|
while a new peak at 550 nm appeared. Although small-molecule fluorescent probes possess numerous opportunities for in situ ion-level detection, their applications in NDDs still remain in preclinical stages due to the limited penetration depth.\[42\]

**Table 1.** Continued.

| Detected ions | Structures of fluorescent probes (functional groups illustrated by the red boxes) | Mechanisms | Detection limit | Applications | Ref. |
|---------------|--------------------------------------------------------------------------------|------------|----------------|--------------|-----|
| Zn\(^{2+}\)  | [Image of Zn\(^{2+}\) compound] | Based on intramolecular charge transfer (ICT) | 50 pM | NIH3T3 fibroblasts | [44] |
| D–π–A–π–D system | [Image of D–π–A–π–D system] | | 15 nM | SHSY-5Y cells | Brain tissue, zebrafish | [45] |

**Figure 2.** Small-molecule fluorescent probes for the detection of Na\(^{+}\), Fe\(^{2+}\), Cu\(^{2+}\), and Zn\(^{2+}\) in cells or tissues. a) The structure of NaGY-AM and its application in monitoring Na\(^{+}\) in HeLa cells. b) The structure of FIP-1 and its application in monitoring Fe\(^{2+}\) in MDA-MB-213 cells. c) The mechanism of S1 detecting Cu\(^{2+}\) and its application in monitoring Cu\(^{2+}\) in MCF-7 cells. d) The structure of P–Zn and its application in monitoring Zn\(^{2+}\) in brain tissue and zebrafish. Parts (a,b): Reproduced with permission.\[36,38\] Copyright 2020, The Royal Society of Chemistry; Copyright 2015, The Royal Society of Chemistry; Copyright 2016, American Chemical Society. Part (c): Reproduced with permission.\[41\] Copyright 2019, The Royal Society of Chemistry. Part (d): Reproduced with permission.\[45\] Copyright 2017, American Chemical Society.
3.2.2. Nanosensors-Based In Situ Analysis

In addition to small-molecule fluorescent probes, nanosensors represent another excellent platform for in situ ion-level detection. For example, carbon dots have attracted extensive attention in ion-level detection via colorimetric and fluorimetric sensing with the proposed mechanisms, including coordination/complexation, inner filter effect, light-induced electron transfer, ion binding, and/or aggregation.[46] Based on B, N, S-co-doped carbon dots, intracellular Fe\(^{3+}\) in HeLa cells could be monitored via colorimetric and fluorescent dual mode.[47] Recently, multiple well-designed nanosensors have been developed and applied in brain disease. For example, our group developed a specific K\(^+\) nanosensor, consisted of K\(^+\)-permeable membranes, mesoporous silica nanoparticles, and commercial K\(^+\) probes, to monitor the small fluctuations of extracellular K\(^+\) concentration in the brain of freely moving animals. Owing to the specific K\(^+\)-permeable membranes, the nanosensor could selectively capture K\(^+\) and achieve timely monitoring the dynamic changes in extracellular K\(^+\) concentration for the diagnosis of epilepsy (Figure 3a).[48] Moreover, a near-infrared-triggered K\(^+\)-selective nanosensor has been engineered by K\(^+\)-permeable membranes, upconversion nanoparticles (UCNPs), and commercial K\(^+\) probes, which could detect K\(^+\) efflux in HEK 293 cells induced by K\(^+\) efflux stimulators, and applied in optical imaging of cortical spreading depression in mice (Figure 3b).[49] In addition, a Zn\(^{2+}\) fluorescent nanosensor engineered by assembling chromophores into UCNPs could detect the Zn\(^{2+}\) based on FRET process in the diagnosis of AD (Figure 3c).[50] In addition, Satoshi et al. fabricated the magnetic calcium-responsive nanoparticles via mixing the lipid-coated iron oxide nanoparticles with fused C2 domains of synaptotagmin 1, which could monitor the dynamic changes in Ca\(^{2+}\) in the living brain via a T\(_2\)-weighted magnetic resonance imaging (MRI) (Figure 3d).[51] In addition, based on the interactions between analytes and nanoscale-sized pores, nanopore sensing has also been used to detect metal ions. For instance, an innovative enzymatic reaction-based nanopore sensing has been developed for detecting Zn\(^{2+}\) selectively and sensitively.[52] Overall, ion-selective nanosensors have demonstrated a good prospect in monitoring ions in the pathophysiological processes of NDDs.

4. Future Opportunities

Based on the crucial roles that ions play in the physiological and pathological processes of NDDs, ion-level detection represents a promising approach for the effective diagnosis. In this section, the perspective applications of ion-level detection for NDDs, including the early diagnosis, in-depth mechanism investigation, and accurate staging, are focused on and discussed (Figure 4).

4.1. Early Diagnosis

The diagnosis of NDDs is currently based on clinical symptoms.[53] However, the neurological abnormalities have emerged for several years. The drugs are anticipated to be more effective when they are administrated at the early stage. Therefore, it is crucial to achieve the early diagnosis and interventions of NDDs. Increasing evidences have proved that Fe\(^{2+/3+}\), Cu\(^{2+}\), Zn\(^{2+}\), and so on are tightly associated with the development of pathologic changes, such as pathological protein, mitochondrial dysfunction, and oxidative stress, indicating that these ions are potential diagnostic markers in the early diagnosis of NDDs. Therefore, ion-level detection may mirror abnormal intracellular activities in neurons, which presents a promising approach to improve the early diagnosis. Recently, ingenious nanosensors focused on Zn\(^{2+}\), Cu\(^{2+}\), and others have been reported to exhibit high performance with satisfying sensitivity and selectivity for efficient diagnosis of AD.[50] Collectively, it is promising for ion-level detection to be capable of effective early diagnosis of NDDs via ion-selective probes and sensors.

4.2. In-Depth Mechanism Investigation

Although many hypotheses have been proposed for the pathogenesis of NDDs, the detailed mechanism remains unclear. Along with progressive development, multiple pathological indicators show dynamic changes, which require real-time and accurate methods to monitor the pathological changes. At present, however, most protein analysis and molecular testing for lesions can only be realized in vitro, in which there are limitations in chronergy and accuracy for in-depth mechanism investigation. Detecting the in vivo dynamic changes in ions is expected to enable the monitoring of NDDs progression in real time, and may reveal the correlation between ion dyshomeostasis and other pathological factors, which contributes to explore the in-depth mechanism of neuron death.

4.3. Accurate Staging

The disease staging plays a key role in evaluating the progression of NDDs. For example, three stages of AD are defined based on clinical symptoms, including the preclinical, mild cognitive impairment, and dementia.[54] In addition, proposed by Braak, the stages of PD are 1) autonomic and olfactory disturbances; 2) sleep and motor disturbances; and 3) emotional and cognitive disturbances, classified by inclusion of body pathology.[55] A more accurate staging of NDDs is needed for a better guidance on the diagnosis and treatment. In comparison with the current classification methods for NDDs, a more accurate and objective classification strategy should be proposed based on specific pathological changes occurring at the early stage of NDDs. Ions play a key role in the occurrence and development of NDDs, especially at the early stage. Encouragingly, highly sensitive and selective K\(^+\) nanosensors have been developed and applied in dynamically monitoring the ion levels of freely moving mice undergoing epilepsy,[48,56] showing great potential in highly accurate and objective staging of NDDs at the molecular level.

Admittedly, there are still challenges for ion-level detection in NDDs. For example, considering their limited penetration across the BBB and insufficient sensitivity, it is not easy for the ion-selective probes or sensors to precisely detect the extremely small ion fluctuations in brain lesions in the early stage. In addition, it is very difficult to accurately monitor the dynamic changes in ions and/or other pathological events in the living brain, which restricts the in-depth mechanism investigation of NDDs. Moreover, the limited sensitivity and selectivity of ion-level detection make the accurate staging relatively difficult due to the small signal fluctuations in the
occurrence and development of NDDs. Further improvements of ion-level sensors with enhanced targeting and sensitivity via rational chemical design and surface engineering are highly demanded, and it is anticipated that ion-level detection continues to be a powerful method to overcome aforementioned challenges in the future.

Furthermore, novel integrated imaging techniques, e.g., positron emission tomography/MRI that can simultaneously export anatomical information and pathological protein levels in the brain, have been emerged as promising future directions to monitor multiple pathological changes in NDDs. Consequently, rationally designed multifunctional imaging probes are also expected to be developed for multimodal imaging-based early diagnosis and mechanism investigation of NDDs.

5. Conclusion

In conclusion, ion dyshomeostasis is a potentially effective prognostic marker for NDDs, and ion-level detection in the brain has
a broad prospect for the early diagnosis, in-depth mechanism investigation, and accurate staging of NDDs. The rationally designed ion-selective probes and sensors with high sensitivity, selectivity, and accuracy are expected to significantly improve the diagnosis of NDDs.

Acknowledgements
This work was supported by the National Key Research and Development Program of China (grant no. 2016YFA0203600), the National Natural Science Foundation of China (grant nos. 31822019, 32071374, 91859116, and 81761148029), One Belt and One Road International Cooperation Project from Key Research and Development Project of Zhejiang Province (grant no. 2019C04024), the Zhejiang Provincial Natural Science Foundation (grant no. LGF19C100002), and the Fundamental Research Funds for the Central Universities (grant no. 2020FZZX001-05).

Conflict of Interest
The authors declare no conflict of interest.

Keywords
diagnosis, ion-level detection, nanosensors, neurodegenerative diseases, small-molecule fluorescent probes

Received: January 4, 2021
Revised: March 17, 2021
Published online:

[1] M. A. Zoroddu, J. Aaseth, G. Crisponi, S. Medici, M. Peana, V. M. Nurchi, J. Inorg. Biochem. 2019, 195, 120.
[2] C. Andreini, I. Bertini, G. Cavallaro, G. L. Holliday, J. M. Thornton, J. Biol. Inorg. Chem. 2008, 13, 1205.
[3] N. Nelson, EMBO J. 1999, 18, 4361.
[4] a) L. Mezzaroba, D. F. Alfieri, A. N. Colado Simao, E. M. Vissoci Reiche, Neurotoxicology 2019, 74, 230; b) Z. Xie, H. Wu, J. Zhao, Neurotoxicology 2020, 80, 112; c) J. McDaid, S. Mustaly-Kalini, G. E. Stutzmann, Cells 2020, 9, 2635.
[5] a) A. K. Srivastava, A. Dev, S. Karmakar, Environ. Chem. Lett. 2017, 16, 161; b) X. Tian, Y. Zhao, Y. Li, C. Yang, Z. Zhou, Sens. Actuators B 2017, 247, 139; c) Z. H. Lin, G. Zhu, Y. S. Zhou, Y. Yang, P. Bai, J. Chen, Z. L. Wang, Angew. Chem. Int. Ed. 2013, 52, 5065.
[6] W. A. Catterall, M. J. Lenaeus, T. M. Gamal El-Din, Annu. Rev. Pharmacol. Toxicol. 2020, 60, 163.
[7] P. Rivas-Ramirez, A. Reboreda, L. Rueda-Ruaza, S. Herrera-Perez, J. A. Lamas, Int. J. Mol. Sci. 2020, 21, 5796.
[8] S. B. Campbell, R. Mackinnon, Science 2005, 309, 897.
[9] B. Pevzner, S. S. Jankauskas, V. A. Babenko, S. D. Zorov, A. V. Balakireva, M. Juhaszova, S. J. Sollott, D. B. Zorov, Anal. Chem. 2018, 552, 50.
[10] F. H. Yu, W. A. Catterall, Genome Biol. 2003, 4, 207.
[11] a) M. C. D'Adamo, A. Liantonio, E. Conte, M. Pessia, P. Imbrici, Neuroscience 2020, 440, 337; b) A. Buchin, A. Chizhov, G. Huberfeld, R. Miles, B. S. Gutkin, J. Neurosci. 2016, 36, 11619.
[12] N. M. Allen, S. Weckhuyzen, K. Gorman, M. D. King, H. Lerche, Eur. J. Paediatr. Neurol. 2020, 24, 105.
[13] M. Scholefield, S. J. Church, J. Xu, S. Kassab, N. J. Gardiner, F. Roncaroli, N. M. Hooper, R. D. Unwin, G. J. S. Cooper, Metallomics 2020, 12, 952.
[14] a) M. Sanchez, L. Sabio, N. Galvez, M. Capdevila, J. M. Dominguez-Vera, IUBMB Life 2017, 69, 382; b) T. J. Zerk, P. V. Bernhardt, Coord. Chem. Rev. 2018, 375, 173.
[15] F. Bulcke, R. Dringen, I. F. Scheiber, Adv. Neurobiol. 2017, 18, 313.
[16] M. C. Leal, R. I. L. Catarino, A. M. Pimenta, M. R. S. Souto, Neurophysiology 2020, 52, 80.
[17] M. E. Letelier, A. M. Lepe, M. Faundez, J. Salazar, R. Marin, P. Aracena, H. Speisky, Chem. Biol. Interact. 2005, 151, 71.
[18] G. Vazquez, A. B. Caballero, J. Kokinda, A. Hijano, R. Sabate, P. Carnez, J. Biol. Inorg. Chem. 2019, 24, 1217.
[19] M. F. C. Leal, R. I. L. Catarino, A. M. Pimenta, M. R. S. Souto, T. S. N. Pinheiro, Quim. Nova 2012, 35, 1985.
[20] N. K. Isaev, E. V. Stelmashook, E. E. Genrikhs, Rev. Neurosci. 2020, 31, 233.
[21] R. P. L. Van Swelm, J. F. M. Wetzel, D. W. Swinkels, Nat. Rev. Nephrol. 2020, 16, 77.
[22] C. C. Philpott, S. JadHAV, Free Radic. Biol. Med. 2019, 133, 112.
[23] S. R. D’Mello, M. C. Kindy, Exp. Biol. Med. 2020, 245, 1444.
[24] D. S. Albers, M. F. Beal, J. Neural. Transm. Suppl. 2000, 59, 133.
[25] A. S. Dickerson, J. Hansen, O. Gredal, M. G. Weisskopf, Int. J. Environ. Res. Pub. Health 2020, 17, 21.
[26] P. Jadiya, D. W. Kolmetzky, D. Tornar, A. Di Meco, A. A. Lombardi, J. P. Lambert, T. S. Luongo, M. H. Ludtmann, D. Pratico, J. W. ELrod, Nat. Commun. 2019, 10, 3885.
[27] V. Tedeschi, T. Petrozziozello, A. Secondo, Cells 2019, 8, 1216.
[28] M. Bisaglia, L. Bubacco, Biomolecules 2020, 10, 195.
[29] Y. Nakagawa, S. Yamada, Pharmacol. Ther. 2020, 207, 107455.
[30] a) M. E. Letelier, M. Martinez, V. Gonzalez-Lira, M. Faundez, P. Aracena-Parks, Chem. Biol. Interact. 2006, 164, 39; b) K. Pamp, T. Bramey, M. Kirsch, H. De Groot, F. Petrat, Free Radic. Res. 2005, 39, 31; c) L. Vujisic, D. Krstic, K. Krunilovic, V. Vasic, J. Serbian Chem. Soc. 2004, 69, 541.
[31] N. K. Isaev, E. V. Stelmashook, E. E. Genrikhs, Rev. Neurosci. 2020, 31, 233.
[32] R. C. Balachandran, S. Mukhopadhyay, D. McBride, J. Veevers, F. E. Harrison, M. Aschner, E. N. Haynes, A. B. Bowman, J. Biol. Chem. 2020, 295, 6312.
[33] C. Grochowski, E. Blicharska, P. Krukow, K. Jonak, M. Maciejewski, D. Szczepanek, K. Jonak, J. Flieger, R. Maciejewski, Front. Chem. 2019, 7, 115.
Ying Chen received her M.Sc. degree (2019) from the Institute of Materia Medica, Chinese Academy of Medical Sciences & Peking Union Medical College. She is currently a Ph.D. candidate in the College of Pharmaceutical Sciences at Zhejiang University under the guidance of Professors Daishun Ling and Fangyuan Li. She works on functional nanomaterials for the diagnosis and therapy of neurodegenerative diseases.

Fangyuan Li received her Ph.D. degree (2015) from the School of Chemical and Biological Engineering, Seoul National University. Since joined the faculty of the College of Pharmaceutical Sciences in Zhejiang University in 2015, she has been focusing on the designed synthesis of functional biomaterials and their medical applications, including medical imaging, drug delivery, and photodynamic therapy.

Daishun Ling received his Ph.D. degree (2013) from the School of Chemical and Biological Engineering, Seoul National University. Later, he joined the faculty of the College of Pharmaceutical Sciences, Zhejiang University. Currently, he is a full professor in School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University. His primary research interest focuses on the assembly/disassembly chemistry, stimuli-responsive biomaterials, and dynamic nanoassembly based drug delivery systems. Up to now, he has published more than 100 papers in prominent international journals, including Nature Nanotechnology, Nature Materials, Nature Biomedical Engineering, Nature Communications, Journal of the American Chemical Society, Angewandte Chemie International Edition, Advanced Materials, and so on.