RSC Chemical Biology

ROYAL SOCIETY OF CHEMISTRY

REVIEW

View Article Online
View Journal | View Issue

Cite this: *RSC Chem. Biol.*, 2023, 4, 548

Transition metal ions and neurotransmitters: coordination chemistry and implications for neurodegeneration

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Received 9th April 2023,
Accepted 26th June 2023

DOI: 10.1039/d3cb00052d

rsc.li/rsc-chembio

Neurodegeneration is characterized by a disturbance in neurotransmitter-mediated signaling pathways. Recent studies have highlighted the significant role of transition metal ions, including Cu(I/II), Zn(II), and Fe(II/III), in neurotransmission, thereby making the coordination chemistry of neurotransmitters a growing field of interest in understanding signal dysfunction. This review outlines the physiological functions of transition metal ions and neurotransmitters, with the metal-binding properties of small molecule-based neurotransmitters and neuropeptides. Additionally, we discuss the structural and conformational changes of neurotransmitters induced by redox-active metal ions, such as Cu(I/II) and Fe(II/III), and briefly describe the outcomes arising from their oxidation, polymerization, and aggregation. These observations have important implications for neurodegeneration and emphasize the need for further research to develop potential therapeutic strategies.

Introduction

Signal transmission is crucial to maintain homeostasis in central and peripheral nervous systems.[1–3] This process relies on neurotransmitters to regulate membrane potentials, biological cascades, or gene expression, which ultimately controls neuronal growth, differentiation, and cell proliferation.[1–3] The accuracy of synaptic functions depends on the precise release of neurotransmitters in response to neural activity, which is largely regulated by biochemical signaling for efficient information processing. Although the relationship between neurotransmitter dysregulation and neurodegeneration remains a controversial topic, some studies suggest that disrupting the production, concentration, and metabolism of neurotransmitters may contribute to the development of neurodegeneration.[4–8]

Extensive research has been conducted on the involvement of alkali and alkaline earth metal ions in signal transmission.[9,10] Na^+ and K^+ regulate the electrochemical gradient across neuronal membranes to generate and propagate action potentials.[9] In addition, Ca^{2+} serves as a second messenger in the phosphoinositol pathway to mediate stimulus-responsive reactions in cells.[10] Transition metal ions, such as Cu(I/II), Zn(II), and Fe(II/III), also play a crucial role in physiological systems. These metal ions function as cofactors in the active sites of metalloenzymes and assist in the structural folding of proteins.[11–15] Moreover, in neurotransmission, transition metal ions facilitate the biosynthesis of neurotransmitters, coordinate with biomolecules, and even act as neurotransmitters themselves.[13,16–18] The colocalization between transition metal ions and neurotransmitters has led to significant interest in their potential inter-communication and impact on neurotransmission.[13,16–23] This review overviews the physiological roles of transition metal ions, their coordination with neurotransmitters, and the subsequent structural or conformational changes in neurotransmitters, with particular emphasis on their potential implications in neurodegeneration.

Physiological roles of Cu(I/II)

Copper, which exists in two major oxidation states Cu(I) and Cu(II), has multiple coordination numbers and geometries.[24] As a result, Cu(I/II) can serve as a catalyst in biological systems. The possible geometries for d^{10} Cu(I) are two-coordinate linear, three-coordinate trigonal planar, and four-coordinate tetrahedral. In the case of d^9 Cu(II), four-coordinate square planar, five-coordinate trigonal bipyramidal, and six-coordinate octahedral geometries are observed, the latter of which is often distorted by Jahn–Teller distortion effects.[25] The redox ability of copper changes its electronic configuration, which makes it have different coordination modes.[24,25]

In biological systems, the ligand environment of static Cu(I/II) pools varies depending on enzymatic functions, such as antioxidant defense and the synthesis of neurotransmitters.[26–29]

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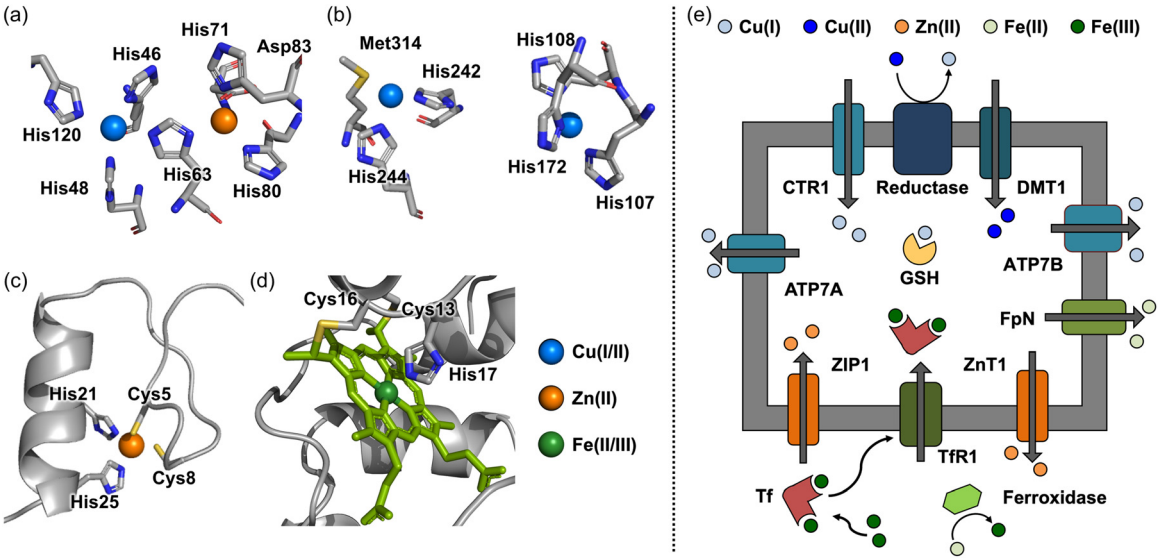

Fig. 1 Coordination of metal ions found in metalloproteins and metal transport across cellular membranes. (a)–(d) Cu(II), Zn(II), and Fe(II/III) coordination found in Cu/Zn SOD (amino acid residues are numbered according to human cytoplasmic Cu/Zn SOD although the coordinates used were those of the bovine enzyme) (PDB 2SOD[26]), peptidylglycine α-hydroxylating monooxygenase (structural analog of DβM) (PDB 1PHM[28]), zinc fingers (PDB 1SP1[44]), and cytochrome *c* (PDB 1C2R[62]). (e) Uptake and release of Cu(I/II), Zn(II), and Fe(II/III) across cellular membranes through metal transporters. Examples of metal transporters include CTR1, DMT1, ATP7A, and ATP7B for Cu(I/II) transport, ZIP1 and ZnT1 for Zn(II) transport, and TfR1 and FpN for Fe(II/III) transport. Copper, zinc, and iron are depicted in blue, orange, and green, respectively.

The concentration of Cu(I/II) has been reported to be ranging from 60 to 110 μM in human frontal lobes and cerebellums.[30] As depicted in Fig. 1a, for instance, superoxide dismutase (SOD) coordinates Cu(II) with four His residues (His46, His48, His63, and His120) to form a distorted square planar geometry.[26] This structural flexibility between square planar and tetrahedral geometries [for Cu(II) and Cu(I), respectively] allows for rapid redox reactions against superoxide anion radicals ($O_2^{-\bullet}$) with a minimal reorganization energy.[26,29] Copper is also found in the active site of dopamine-β-monooxygenase (DβM), which is responsible for the biosynthesis of dopamine (DA).[27,28] DβM comprises two copper centers, as described in Fig. 1b: (i) one sulfur (S) donor atom and two nitrogen (N) donor atoms from Met487, His412, and His414, respectively; (ii) three N donor atoms from His262, His263, and His333.[27,28] Such differences in the coordination sphere can be correlated with distinct functions at each copper center. The formal one with 2N1S coordination initiates the oxidation of DA *via* reducing O_2 to $O_2^{-\bullet}$, while another copper center provides an additional one electron to terminate the whole reaction.[27,28] While the coordination chemistry of static copper sites in metalloenzymes has been extensively studied, the existence and functions of labile copper pools have been relatively less understood.[31–34] Recent studies have shown the presence of endogenous labile copper pools in cultured hippocampal neurons and retinal tissue slices, suggesting the potential role of labile copper in regulating normal neuronal functions.[32,34–36] Interestingly, labile copper can also behave as a neurotransmitter modulator. For example, copper can regulate neurotransmission by acting as an antagonist of γ-aminobutyric acid (GABA) receptors upon binding to the His residues located in the extracellular domain.[20,37–39]

Physiological roles of Zn(II)

Zn(II) is found in biological systems (at approximately 150 μM in the brain).[30] The coordination number varies from four to six with tetrahedral and octahedral geometries being the most common.[40,41] Zn(II) has a closed d-shell, resulting in uniform ligand field stabilization energy (LFSE), making it thermodynamically stable even when it undergoes changes in the geometry or coordination number.[42] The distinct d^{10} electron configuration of Zn(II) is explained for its role in the structural folding and stability of metalloproteins.[42]

Unlike Cu(I/II), which drives electron-transfer reactions (*vide supra*), Zn(II) primarily functions to organize and stabilize the structures of proteins, such as zinc finger proteins.[43,44] As depicted in Fig. 1c, Zn(II) in zinc finger proteins is coordinated to four Cys or His residues in a tetrahedral geometry, forming $Zn(II)(Cys)_2(His)_2$, $Zn(II)(Cys)_3(His)$, and $Zn(II)(Cys)_4$. It should be noted that Asp and Glu can also be part of the coordination spheres.[43,44] Zn(II) binding to zinc finger proteins enables interactions with nucleic acids, which allows them to function as a transcription factor.[45,46] In addition, Zn(II) can act as a Lewis acid that can activate nucleophiles.[40,47,48] For instance, the Zn(II) center in carboxypeptidase A is coordinated with two N donor atoms and one O donor atom from His69, His196, and Glu72, respectively, which facilitates the deprotonation of a water molecule in the coordination sphere of carboxypeptidase A to catalytically hydrolyze amide bonds of peptides.[49] In addition, Zn(II) has been reported to modulate neurotransmission, with one well-documented example being its inhibitory effect on the $GABA_A$-activated current.[38,50] Although the detailed mechanism remains unclear, it has been suggested that Zn(II) coordination to

Glu137 and His141 in the α_1 subunit, and Glu182, His267, and Glu270 in the β_3 subunit may be involved.[38,50] As a neurotransmitter itself, Zn(II) is co-released with glutamate to modulate the excitatory neurotransmission, and it is involved in learning and memory.[51] For example, the lowered levels of Zn(II) can induce hippocampus-dependent memory deficits, mediated by decreasing the activation of extracellular signal-regulated kinases 1 and 2 (Erk1/2).[51]

Physiological roles of Fe(II/III)

Iron is the most available transition metal in biological systems (at approximately 720 μM in normal brains), and it participates in a wide range of enzymatic reactions.[30,52,53] Iron can accommodate multiple oxidation states, such as Fe(II), Fe(III), and Fe(IV), under physiological conditions.[54] The coordination number of Fe(II/III) is commonly observed to be six with an octahedral geometry, but three-coordinate trigonal planar, four-coordinate tetrahedral or square planar, and five-coordinate trigonal bipyramidal geometries are also found on the iron centers.[55–57] As expected from various geometries and oxidation states of iron, it is utilized in a broad range of redox-mediated reactions, including oxygen transfer, electron transfer chain, and the biosynthesis of neurotransmitters.[52,58] For instance, heme proteins are a prime example of iron-based electron transfer systems, where heme is the structural framework composed of iron coordinated to a porphyrin ligand with a 4N coordination mode.[59] In cytochromes, heme is bound to a Cys-Xxx-Xxx-Cys-His motif, and the internal His residue is considered as an additional axial ligand with either Met or Tyr.[60–62] As depicted in Fig. 1d, cytochrome *c* containing a heme moiety transfers an electron from complex III to complex IV, generating a proton gradient across the mitochondrial membrane and producing adenosine triphosphate (ATP).[60–62] Iron–sulfur clusters represent another example of iron's use in electron transfer.[58,63,64] By virtue of the redox properties of iron, thiolates are bridged to iron(s) with different ratios, producing 2Fe–2S, 3Fe–4S, and 4Fe–4S clusters that are associated with nitrogen fixation, oxidative phosphorylation, mitochondrial respiratory pathways, and ribosome assembly.[58,63,64] Additionally, iron is involved in the production of neurotransmitters. In particular, the biosynthesis of catecholamine-based neurotransmitters is highly dependent on the reaction of iron-containing hydroxylase (*e.g.*, phenylalanine hydroxylase that coordinates with Fe(II) through two His residues and one Glu residue).[65] The role of iron as a neurotransmitter has not been well elucidated; however, several reports have indicated that iron is highly related to dopaminergic systems and anxiety-like behaviors.[16,66,67] Moreover, ferroptosis caused by the imbalance of iron species is implicated to be the pathogenesis of neurodegeneration.[16,66–71]

Metal ion homeostasis

Transition metal ions, such as Cu(I/II), Zn(II), and Fe(II/III), are essential for physiological functions in the brain and neurotransmission (*vide supra*).[13,16–23] The uptake and release of these elements are tightly regulated by metal transporters and metallochaperones, as illustrated in Fig. 1e. In this review, we briefly overview the influx and efflux of Cu(I/II), Zn(II), and Fe(II/III). Other review papers are available for detailed information.[17,21,48,51,66,67,72–74]

Copper uptake protein 1 (CTR1) is a representative transporter that involves almost 70% of total copper import into the brain.[72] X-ray absorption spectroscopic studies revealed that the human CTR1 trimer binds two Cu(I) through three-coordinate Cu–S bonds within the Met-Xxx-Xxx-Xxx-Met motif, providing a copper channel.[75,76] Intracellular copper is then appropriately delivered to target enzymes, such as cytochrome *c* oxidase (C*c*O) and SOD, by metallochaperones, including COX17 (for C*c*O) and CCS (for SOD), or stored in glutathione (GSH).[72,77] Excess copper is removed from brain cells into the cerebrospinal fluid (CSF) followed by being stored in ATP7B for potential transport to the CSF or transported into the blood by ATP7A.[72,78]

Zn(II) homeostasis is maintained by several transporters, such as Zrt-, Irt-like protein (ZIP) and zinc transporter (ZnT) proteins.[48,51,73] ZIP8, ZIP10, and ZIP14 are mainly linked to the uptake of Zn(II), while ZnT1 and ZnT10 manage its efflux. ZnT3 transports Zn(II) from the cytosol into synaptic vesicles.[48,51,73] These transporters coordinate to Zn(II) *via* three oxygen (O) donor atoms and one N donor atom from three carboxylate groups in Asp and one imidazole group in His.[73,79]

In the case of iron, once exported from endothelial cells to the interstitial fluid through ferroportin (FpN), Fe(II) is transferred into neuronal cells through divalent metal transporter 1 (DMT1), or it is oxidized to Fe(III) by ceruloplasmin (Cp) to undergo a transferrin (Tf)-mediated pathway.[53,67] Tf is composed of two domains and coordinates to two Fe(III).[80] Fe(III) is coordinated to Tf through five O donor atoms from Asp63, Tyr95, Tyr188, and CO_3^{2-}, and one additional N donor atom from His249, forming an octahedral geometry.[80] The coordination of CO_3^{2-} onto the Fe(III) center induces the conformational difference between apo-Tf and holo-Tf, which can be recognized by Tf receptor 1 (TfR1).[80] Fe_2Tf bound to TfR1 can be internalized *via* endocytosis.[81] The activation of proton pumps can lower endosomal pH to around 5.6, and the reduction of Fe(III) to Fe(II) directs the dissociation of Fe(II) from Fe_2Tf.[81] The released Fe(II) is stored as its oxidized form, Fe(III), in ferritin for future use in biological systems.[81]

Small molecule-based neurotransmitters and their metal-mediated chemical transformations

Small molecule-based neurotransmitters are associated with the regulation of both physiological and behavioral processes through neurotransmission.[82,83] These neurotransmitters can be derived from a single amino acid residue.[83] Monoamine-based neurotransmitters synthesized from Tyr or Phe possess a distinct structure featuring an amino group linked to an aromatic ring by an ethylene linker.[82,83] Interestingly, some amino acids themselves can act as neurotransmitters, such as Glu,

Asp, Gly, Trp, and Phe, which are directly or indirectly involved in signaling pathways.[83] This section illustrates the physiological functions of Tyr, Trp, and Phe-derived neurotransmitters that are known to interact with transition metal ions and, subsequently, undergo structural transformations.

Dopamine

Dopamine (DA) is a monoamine-based neurotransmitter categorized as a catecholamine, as presented in Fig. 2a.[84] The gradual loss of DA-producing neurons in the substantia nigra is believed to contribute to Parkinson's disease (PD); thus, efforts have been made to elucidate the role of DA in neurodegenerative disorders.[84–86] DA is primarily involved in four axonal pathways: nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular, initiating physiological responses for the control of movement, learning and memory, motivated behavior, attention, emotion, milk production, and lactotroph proliferation.[84] Particularly in PD, however, the degeneration of dopaminergic neurons can reduce the production and release of DA, resulting in several characteristic motor symptoms, such as tremors, rigidity, bradykinesia, and balance instability.[85–87]

Under aerobic conditions, the catechol moiety shown in DA can be oxidized to quinone [$E_{1/2}$ = 0.801 V *versus* standard hydrogen electrode (SHE)], as depicted in Fig. 2a.[88] Waite and coworkers reported that the oxidation of DA is notably accelerated upon binding to Cu(II) *via* its catechol moiety.[89] This copper–catechol chemistry results in electron transfer, producing Cu(I) and DA$^{\bullet}$, with the latter reducing additional Cu(II) and transforming into dopaquinone.[90] Dopaquinone readily undergoes cyclization to form dopachrome, which is oxidized to the relatively stable dopaminechrome, rearranged into 5,6-dihydroxyindole, and finally converted into 5,6-indolequinone.[89] The oxidation process of DA is characterized by monitoring the absorbance at approximately 475–480 nm, indicating the presence of a dopaminechrome intermediate.[89]

The metal-mediated oxidation of DA summarized in Fig. 2a can induce toxicity. In detail, DA can generate reactive oxygen species (ROS) through Fenton-like reactions (redox reactions between Cu(I) and Cu(II) in the presence of DA and O_2).[91–93] Following similar mechanisms, Fe(II/III) can also generate quinone species and ROS *via* iron–catechol chemistry or Fenton chemistry.[91–93] ROS can cause oxidative stress in cellular systems, resulting in lipid peroxidation and protein misfolding.[93,94] Furthermore, unstable quinone intermediates, such as dopaquinone, dopaminechrome, and 5,6-indolequinone, may induce neurotoxicity *via* the stabilization of toxic oligomers and protofibrils of amyloidogenic proteins (*e.g.*, α-synuclein, a pathological factor associated with PD), mitochondrial dysfunction mediated by adduct formation with complex I, III, and IV, and the disruption of proteasome and lysosomal systems by inactivating the parkin system or simply generating complexes with ubiquitin C-terminal hydrolase L1 (UCH-L1), α-tubulin, and β-tubulin.[95–97] Such adduct formation was suggested to occur *via* Michael addition with polar side chains, such as His, Cys, and Lys.[93] In addition, another DA metabolite, 3,4-dihydroxyphenylacetaldehyde (DOPAL), also stabilizes toxic oligomers and protofibrils of amyloidogenic peptides and proteins [*e.g.*, amyloid-β (Aβ) and α-synuclein], inducing high toxicity.[98]

Interestingly, the neuroprotective roles of DA have continuously been reported by multiple groups.[99–102] For instance, DA can alleviate inflammation and oxidative stress induced by Aβ, a pathological factor associated with Alzheimer's disease (AD).[99,100] Govindaraju and coworkers suggested the neuroprotective properties of DA to mitigate Aβ-mediated toxicity by modulating its aggregation and exhibiting antioxidant activity.[99] Lim and coworkers presented that DA undergoes oxidation when it is incubated with Cu(II) in both the absence and presence of Aβ.[100]

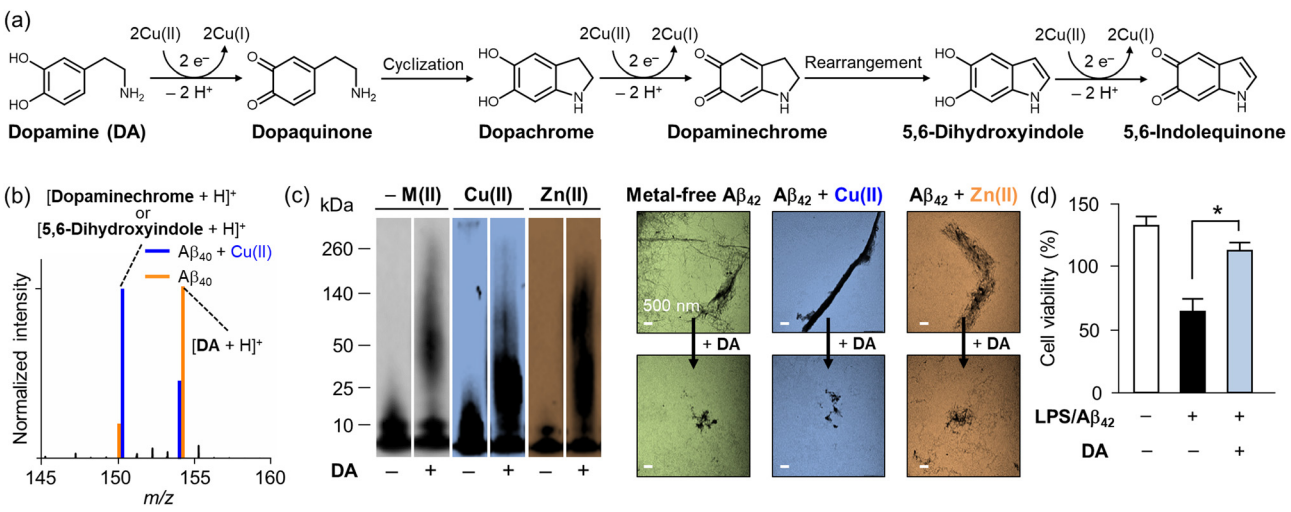

Fig. 2 Impact of Cu(II) on the chemical transformation of DA with its effects on the aggregation and cytotoxicity of Aβ (a) Oxidative transformation of DA in the presence of Cu(II). (b) Analysis of DA transformation in the presence of $A\beta_{40}$ with and without Cu(II) by mass spectrometry. (c) Inhibitory impact of DA on metal-free and metal-added Aβ aggregation *in vitro*. The size distribution and morphology of Aβ aggregates produced with and without DA and metal ions were investigated by gel/Western blot and TEM, respectively. (d) Improvement of cytotoxicity upon incubation with DA. Reproduced with permission from ref. 100 Copyright© 2018 American Chemical Society.

When DA is incubated with metal-free Aβ, the slow oxidation of DA was observed by mass spectrometry, as depicted in Fig. 2b. In the presence of Cu(II) and Aβ, however, the oxidation process of DA is facilitated.[100] Notably, DA can also modulate the aggregation pathway of Aβ incubated with and without Cu(II) and Zn(II), as shown in Fig. 2c. The analysis by gel electrophoresis with Western blotting (gel/Western blot) revealed that DA could modify the aggregation of metal-free and metal-added Aβ, generating amorphous Aβ aggregates that were detected by transmission electron microscopy (TEM). Moreover, as illustrated in Fig. 2d, the treatment of DA alleviated the cytotoxicity triggered by Aβ.[100] Taking account of the coordination mode of Cu(I)–Aβ complexes, His13 and His14 in Aβ have been suggested to provide a platform for Cu(I) coordination.[101] The Cu(I)–Aβ complex interacts with the catechol group of DA and O_2 to give a dopamine *o*-semiquinone radical and $O_2^{-\bullet}$.[101] The dopamine *o*-semiquinone radical can disproportionate with a second semiquinone species, generating dopaquinone and DA.[101] This process results in the oxidation of Aβ at Met35 and its covalent modification with quinone species, which alters Aβ aggregation pathways.[100–102] In summary, both neurotoxic and neuroprotective effects of DA with transition metal ions have been suggested, and further research can provide a better understanding of the role of DA in neurodegeneration.

Tryptophan

Tryptophan (Trp) (Fig. 3a) is one of the 20 amino acids that make up proteins, which is not synthesized in humans but from bacteria, fungi, and plants.[103] Trp is well documented that its supplementation improves sleep quality and maintenance.[104,105] Although the spectroscopic evidence to support the binding of transition metal ions to Trp is very limited, DFT studies have suggested its possible coordination to divalent metal ions, such as Ni(II), Cu(II), and Zn(II), *via* the amine, carboxylate, and ring moieties.[106,107] Interestingly, Trp undergoes several metabolic pathways under physiological conditions, generating essential neurotransmitters, such as 5-hydroxytryptamine (5-HT) and kynurenine (KYN).[108–115] As illustrated in Fig. 3a, Trp can be oxidized to oxyindolylalanine, which is consecutively metabolized into *N*-formylkynurenine and KYN.[114,115] KYN then follows a metabolic pathway, also known as the KYN pathway to generate NAD^+.[108–113] Such KYN pathways have been reported to modulate dopaminergic, nicotinergic, and glutaminergic neurotransmission, which may be related to numerous psychiatric and neurodegenerative symptoms.[108–113,116]

In neurodegeneration, however, the oxidation process of Trp to KYN can be facilitated in the presence of redox-active transition metal ions producing ROS.[114,115] The imbalance in

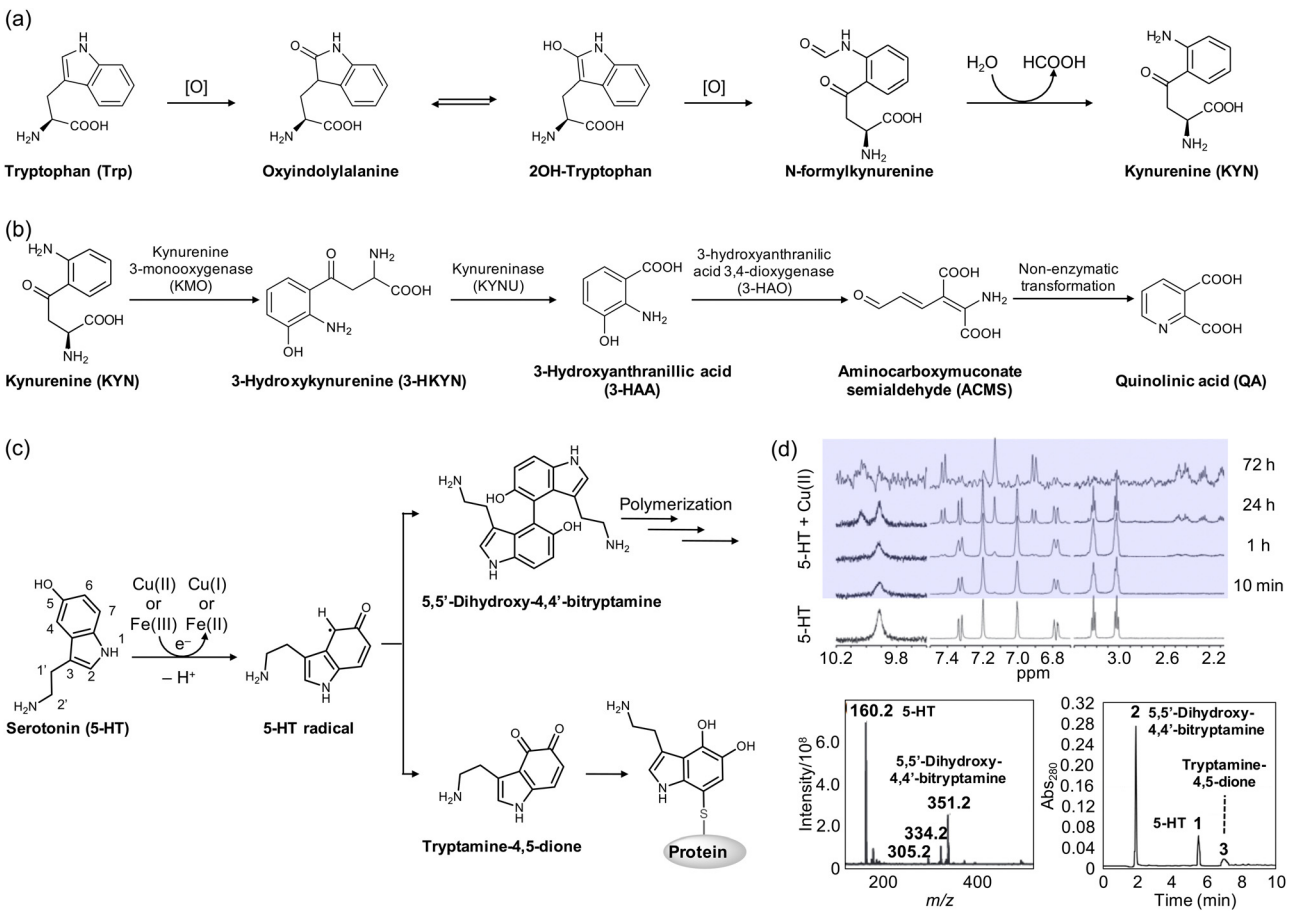

Fig. 3 Structural transformations of Trp and 5-HT. (a) Metabolic pathway of Trp to KYN in the presence of ROS. (b) Metabolites from the KYN pathway. (c) Cu(I/II)-mediated oxidation and polymerization of 5-HT. (d) Oxidized products of 5-HT monitored by ^{1}H NMR spectroscopy, mass spectrometry, and HPLC. Reproduced with permission from ref. 122 and 123 Copyright© 2007 John Wiley and Sons and 2014 Springer Nature.

the KYN concentration can accelerate the KYN pathway, upregulating the overall amount of KYN metabolites.[108–115] Among various metabolites from the KYN pathway illustrated in Fig. 3b, 3-hydroxykynurenine (3-HKYN), 3-hydroxyanthranillic acid (3-HAA), and quinolinic acid (QA) have shown toxicity.[108,109,112] To be specific, 3-HKYN elevates oxidative stress by blocking antioxidant catalases.[108,109,112] QA, on the other hand, exhibits neurotoxicity by stimulating the release of glutamate and inhibiting the astroglial reuptake with the reduced activity of glutamine synthase.[108,109,112] This elevates the extracellular concentration of glutamate and persistently activates excitatory neurons, leading to mitochondrial dysfunction, the release of cytochrome *c*, and the activation of proteases and caspases.[108,109] Interestingly, 3-HAA and QA can generate ROS with the interactions between redox-active transition metal ions, such as Cu(I/II) and Fe(II/III), which promotes neurodegeneration through various effects, including lipid peroxidation.[108–110,112]

Serotonin

Serotonin, also known as 5-HT (Fig. 3c), is a monoamine-based neurotransmitter synthesized in serotonergic neurons in the central nervous system.[117,118] 5-HT is involved in cell growth and differentiation, smooth muscle activity, neuronal development, and signaling pathways.[117,118] Due to these essential functions, it has been suggested that altered serotonergic neurotransmission may contribute to mood, motor, sensory, autonomic, cognitive, and sleep disorders that are commonly found in PD and other neurodegenerative disorders.[3,119] Moreover, studies have shown that 5-HT receptors impact amyloid precursor protein processing into Aβ by activating these receptors, which increases non-amyloidogenic APP processing *in vitro*.[120] Furthermore, the chronic treatment of selective 5-HT reuptake inhibitors, such as citalopram, reduces cerebral Aβ levels in mice, suggesting a potential therapeutic target for neurodegenerative diseases.[121]

In the presence of redox-active transition metal ions, which include Cu(I/II) and Fe(II/III), 5-HT is transformed through an electron-transfer process, as illustrated in Fig. 3c.[122–124] At the initial stage of oxidation, 5-HT is oxidized by one electron to form a 5-HT radical intermediate, which can be detected at approximately 410 nm by electronic absorption spectroscopy.[122] As depicted in Fig. 3d, the treatment of Cu(II) to 5-HT for 24 h resulted in the appearance of new peaks at 6.9, 7.1, and 7.5 ppm in ^{1}H nuclear magnetic resonance (NMR) spectra.[122] In particular, the singlet peak at 7.1 ppm suggested that only one proton exists, derived from either C2 or C4. The disappearance of the 1.9 Hz coupling between C4 and C6 clarified the dimerization of 5-HT *via* coupling of two species at the C4 position.[122] The dehydrogenative coupling of two 5-HT molecules was also supported by mass spectrometry.[122] Heme–Aβ complexes have been found to induce the same dimerization of the 5-HT radical intermediate, as observed by electronic absorption spectroscopy.[123] Alternatively, the 5-HT radical intermediate can be oxidized to tryptamine-4,5-dione. As shown in Fig. 3d, investigations by high performance liquid chromatography (HPLC) showed a minor peak (peak 3), assigned to be tryptamine-4,5-dione produced by the oxidation of the 5-HT radical.[123] Moreover, the 5-HT radical intermediate may subsequently form covalent adducts with thiol groups of proteins and enzymes, including tryptophan hydroxylase.[125–127] This can direct the irreversible loss of function. While the impact of tryptamine-4,5-dione on cytotoxicity is still a topic of debate, some studies have reported that it may upregulate the mRNA and protein expression of NAD(P)H quinone dehydrogenase 1 (NQO1) and heme oxygenase-1 (HO-1) responsible for relieving the cytotoxicity induced by hydrogen peroxide (H_2O_2).[128,129] The transformation of 5-HT in the presence of redox-active transition metal ions can lead to diverse outcomes that require further investigation.

Epinephrine

Epinephrine, also known as adrenaline, plays a key role in physiological muscle contraction, especially in the vascular smooth muscle and intestinal sphincter muscle, upon binding to α_1 and α_2 adrenergic receptors.[130] The activation of β_1 receptors by epinephrine contributes to the increase in heart rate, myocardial contractility, and renin release, while binding to β_2 receptors provokes bronchodilation and glucose metabolism.[130] Chronic stress can alter the level of epinephrine, disrupting the regulation of the stress response and potentially contributing to pathological conditions, such as cancer, cardiovascular dysfunction, and neurodegeneration.[131] Thus, maintaining the proper levels of epinephrine is crucial for overall health and well-being.

The involvement of epinephrine's oxidation in neurodegeneration has received attention as a major contributing factor.[132,133] The oxidation of catecholamines at physiological pH is generally very slow; however, it can be facilitated by enzymatic or metal-mediated catalysis.[134] As illustrated in Fig. 4a, copper–catechol chemistry is involved in the oxidation process, where epinephrine reduces two Cu(II) to generate epinephrinequinone and two Cu(I).[132,135] The structural instability of epinephrinequinone makes it readily cyclized to form leucoepinephrinechrome, or it can coordinate to GSH. Leucoepinephrinechrome, retaining the catechol moiety, undergoes another round of electron-transfer process, leading to epinephrinechrome, which can fall into three different fates: a reverse reaction to leucoepinephrinechrome accompanied by ROS generation, polymerization, or coordination to a thiol moiety of enzymes.[132,135] In particular, the adduct formation between epinephrinequinone and GSH was observed to result in the overall depletion of GSH concentration, causing noxious effects on cellular function and defense.[132] Moreover, 5-(glutathione-*S*-yl)epinephrine has been reported to induce toxicity by activating caspase-3 or oxidizing DNA bases.[136] Rael and coworkers presented that chelating out copper by D-Asp–D-Ala–D-His–D-Lys (D-DAHK) could exert a protective effect from oxidative stress induced by the copper–epinephrine interaction,[134] suggesting that redox-active metal ions are highly related to cytotoxicity in the progression of neurodegeneration.

Phenylalanine & phenethylamine

Phenylalanine (Phe) (Fig. 4b) can be obtained from various food sources, including meat, wheat, and milk products.[137] As a neurotransmitter, Phe is associated with controlling chronic pain, depression, and other disorders.[137] Moreover, Phe is a

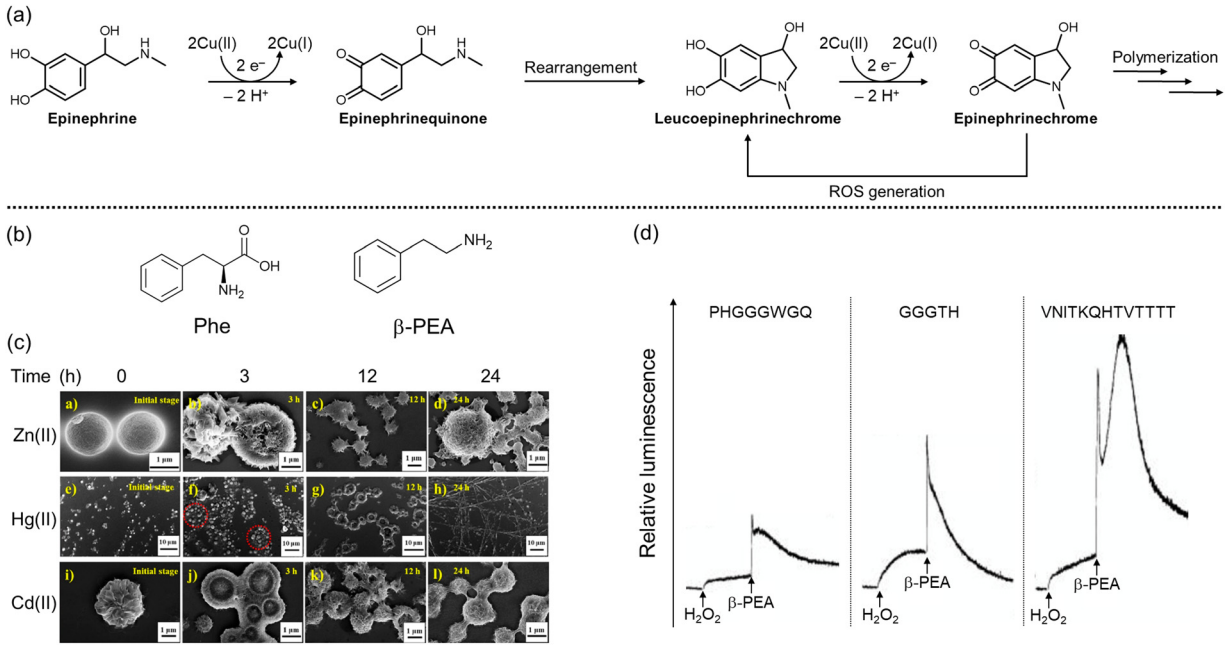

Fig. 4 Structural changes of epinephrine as well as fibrilization and ROS generation of Phe and β-PEA in the presence of divalent metal ions. (a) Oxidation and polymerization of epinephrine in the presence of Cu(II). (b) Chemical structures of Phe and β-PEA. (c) Aggregation of Phe into fibrillar species in the presence of divalent metal ions, including Zn(II), Cd(II), and Hg(II). Reproduced with permission from ref. 141. Copyright© 2022 American Chemical Society. (d) Increased levels of $O_2^{-\bullet}$ by incubation of β-PEA, Cu(II), and fragments of the prion protein. Reproduced with permission from ref. 142. Copyright© 2006 Ivyspring International Publisher.

precursor to monoamine-based neurotransmitters like DA and 5-HT, making its cellular levels indirectly related to signaling pathways.[138] Interestingly, Phe can be decarboxylated by phenylalanine decarboxylase to generate phenethylamine (β-PEA; Fig. 4b),[138] the specific role of which has not been fully elucidated. Several studies, however, suggest that β-PEA is involved in dopaminergic transmission.[139,140] β-PEA inhibits the influx of DA, 5-HT, and norepinephrine by binding to amine-associated receptor 1,[139] while the interaction with the DA receptor stimulates the release of DA in striatal brain slices.[140]

In the presence of metal ions, however, the aforementioned functions of Phe and β-PEA as neurotransmitters begin to diminish, and toxicity arises.[141–144] In the case of Phe, Chakraborty and coworkers presented that divalent and trivalent metal ions, including Zn(II), Cd(II), Hg(II), Al(III), Ga(III), and In(III), could induce the self-aggregation of Phe.[141] The impact of metal ions on Phe aggregation was investigated by confocal laser scanning microscopy and field emission scanning electron microscopy, as shown in Fig. 4c. It should be noted that the production of fibrillar species was monitored by the thioflavin-T (ThT) that is broadly used for quantitative analysis of β-sheet structures.[145] In the presence of divalent metal ions, monomeric Phe rapidly generated microspheres that were fused into vesicular structures and transformed into mature fibrils over time. In particular, in the presence of Zn(II), the fibrils elongated in a dendritic fashion, orienting in one common center.[141] On the other hand, β-PEA could increase the level of $O_2^{-\bullet}$ upon incubation with copper and copper-binding fragments of the prion protein, as presented in Fig. 4d.[142] Alternatively, even in the absence of metal ions, β-PEA could aggravate oxidative stress by inhibiting the activity of NQO1 as well as mitochondrial complex I and complex III.[143,144]

Peptide-based neurotransmitters and their conformational and functional changes mediated by metal ions

Peptide-based neurotransmitters, referred to as neuropeptides, are involved in neuronal signaling associated with analgesia, reward, food intake, metabolism, social behaviors, learning, and memory.[146] Recent advances in biotechnologies coupled with solid-phase peptide synthesis have opened up new avenues for developing peptide-based medicines, which are being actively explored in the therapeutic field against neurodegeneration.[147] Notably, several studies have shown that transition metal ions interact with neuropeptides and distinctively affect signaling pathways, indicating the importance of elucidating how metal coordination influences the physiological and pathological functions involved in neurodegeneration caused by metal ion dyshomeostasis.[148–154] Such a comprehensive understanding can pave the way for novel therapeutic strategies for neurodegeneration. The following section covers recent studies on the coordination chemistry of transition metal ions with neuropeptides, particularly focusing on those containing a disulfide bond: somatostatin (SST), vasopressin (AVP), and oxytocin (Oxt).

Somatostatin

Somatostatin (SST; Fig. 5a) is a naturally occurring neuropeptide composed of 14 amino acid residues (AGCKNFFWKTFTSC)

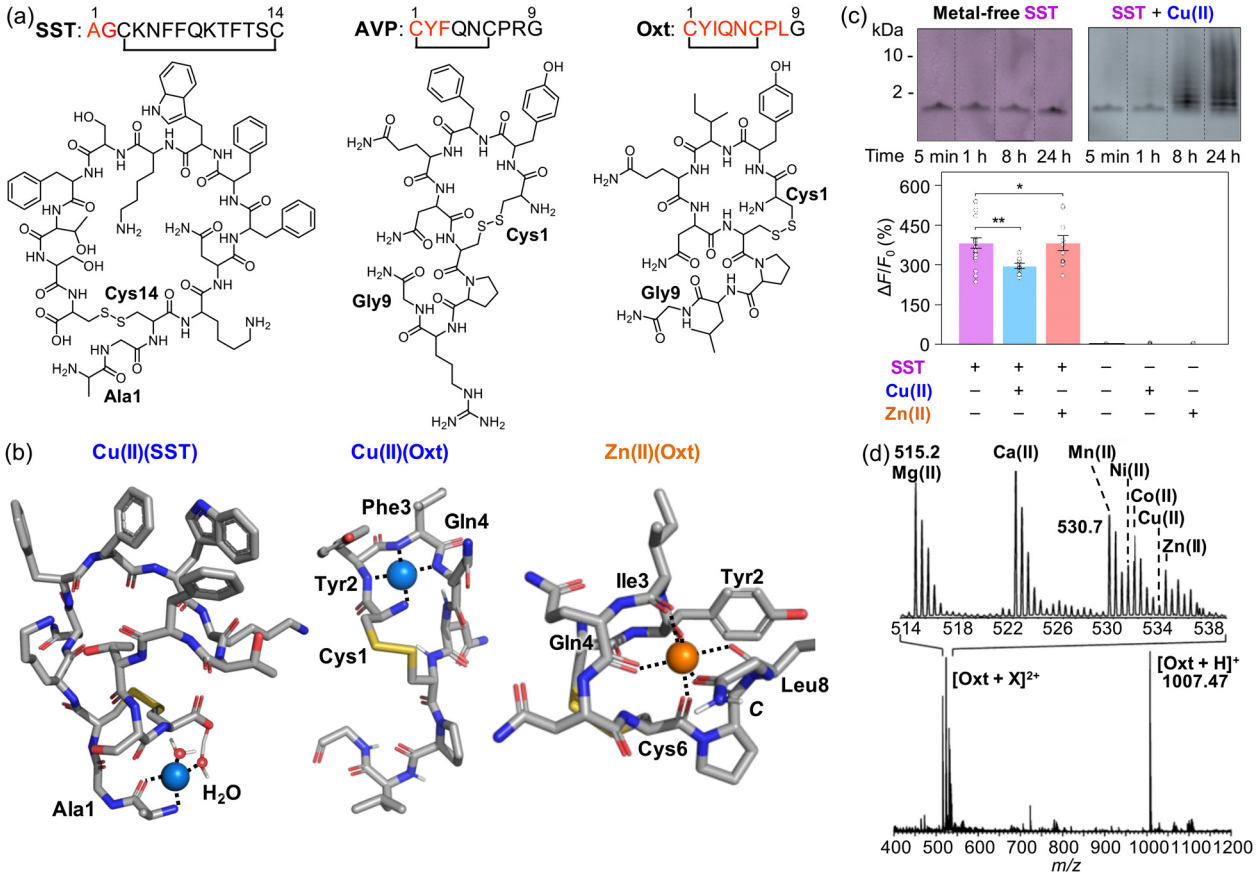

Fig. 5 Interactions of SST, AVP, and Oxt with metal ions. (a) Amino acid sequences and chemical structures of SST, AVP, and Oxt. (b) Potential metal binding to SST and Oxt.[148,152,153] (c) Aggregation and change in the receptor binding of SST in the presence of Cu(II). Reproduced with permission from ref. 148. Copyright© 2022 Springer Nature. (d) Adduct formation between Oxt and various divalent metal ions, including Mg(II), Ca(II), Mn(II), Ni(II), Co(II), Cu(II), and Zn(II). Reproduced with permission from ref. 152. Copyright© 2008 American Chemical Society.

with an intramolecular disulfide bond between Cys3 and Cys14.[155] SST plays a vital role in nervous systems despite its short half-life (around 3 min), inhibiting the secretion of growth hormone (GH) mediated by the growth hormone-releasing hormone (GHRH) from anterior pituitary somatotrophs.[156] In obese patients, GH secretion may be affected, with the subsequent responsivity of SST for suppressing insulin and glucagon.[157] SST can also inhibit adenyl cyclase and Ca(II) channels, leading to the inhibition of cell proliferation,[157] as well as olfactory systems.[158,159] As the homeostasis of SST is impaired, it may behave differently, however.[160,161] In PD patients, the concentration of SST decreases in frontal and temporal cortices, and its colocalization with Lewy bodies is observed, which is thought to be a cause of the disease impacting olfactory systems and non-motor symptoms, such as tiredness, depression, and pain.[162] In the case of AD, SST has been reported to specifically bind toxic $A\beta_{42}$ oligomers.[163,164]

Recently, Lim and coworkers have demonstrated that the presence of Cu(II) could result in the loss of function of SST as a neurotransmitter.[148] Cu(II) was observed to coordinate to the N-terminal primary amine, the backbone carbonyl group between Ala1 and Gly2, and two water molecules, one of which is deprotonated by the C-terminal carboxylate group, as illustrated in Fig. 5b.[148] Cu(II) binding to SST could partially fold the N-terminal region of the peptide, which may be a driving force for its self-assembly *via* hydrophobic interactions, antiparallel β-sheet formation, or the $Cu(II)(SST)_2$ generation. It should be noted that other Cu(II)-binding sites, in addition to the N-terminal region, have also been suggested within the sidechain of Phe6 and Phe7 *via* cation–π interactions.[165]

The formation of SST aggregates upon incubation with Cu(II) was detected by the gel/Western blot, as shown in Fig. 5c.[148] Moreover, SST species produced with Cu(II) were shown to have less binding properties to the receptor, confirmed by the studies employing the GPCR-activation-based sensor ($GRAB_{SST}$).[148] It should be noted that such conformational and functional changes of SST were not observed in the presence of Zn(II).[148] These findings suggested that Cu(II) interaction could cause the aggregation of SST and, consequently, inhibit its receptor binding properties critical for signaling.[148] When SST was incubated with Aβ in both the absence and presence of Cu(II) and Zn(II), the aggregation of SST into oligomers was also observed, resulting in reduced interactions against cell membranes.[148] The co-incubation between metal ions and SST has been shown to mitigate the cytotoxicity mediated by Aβ.[148] Overall, these results and observations suggest the alteration of the structure and activity of SST

under pathological conditions and provide broader insight into the new role of neuropeptides in the pathologies of neurodegenerative diseases.

Vasopressin

Vasopressin (Fig. 5a), also known as arginine vasopressin (AVP), is a nonapeptide neurotransmitter (CYFQNCPRG) that forms a cyclic structure through a disulfide bond between Cys1 and Cys6.[166] AVP is importantly linked to osmoregulation.[166–169] It is also involved in increasing the mean arterial blood pressure by binding to vasopressin type 1 (V1) receptors, which mediates vasoconstriction in the skin, skeletal muscle, and mesenteric blood vessels.[166,170,171] Furthermore, AVP binding to V3 receptors can control thermoregulation, cognition, memory, and behavior regulation.[172,173] The expression levels of AVP are decreased in patients with neurodegenerative disorders, such as Huntington's disease (HD).[174] Interestingly, AVP(4-8) has been shown to improve cognitive function in an AD mouse model,[175] suggesting the involvement of AVP metabolites in neurodegeneration.

An AVP mutant in which the side chain of Phe3 is substituted with naphthalene (Nal) has been found to bind divalent metal ions, including Cu(II), Zn(II), and Mn(II).[149] A different AVP mutant with an additional Ala residue at the N-terminus has demonstrated the same result.[150] Metal coordination to AVP could stabilize its active structure and potentiate its function.[176] Cu(II)-binding residues in AVP have been proposed through CD, electron paramagnetic resonance, and electronic absorption spectroscopies.[150] Cu(II) was observed to coordinate with four N donor atoms, including one from the N-terminal primary amine and three from the amide backbones between Cys1/Tyr2, Tyr2/Phe3, and Phe3/Gln4.[151] Cu(II) coordination to AVP has been suggested to constrain the receptor-binding residues (*e.g.*, Tyr2 and Phe3), which may alter its contractile activity;[151] however, the exact mechanism is still unclear.

Oxytocin

Oxytocin (Oxt; Fig. 5a) is a nonapeptide (CYIQNCPLG) with a cyclic structure formed by the disulfide bond formation between Cys1 and Cys6.[177] Notably, the sequence of Oxt resembles that of AVP, differing only in two amino acid residues (*i.e.*, Ile3 and Leu8). Oxt plays diverse physiological roles in lactation, parturition, memory, recognition, affiliation, aggression, learning, stress, and depression.[177] In addition, Oxt is also involved in cell proliferation, slowing the heart rate, and myoblast fusion with myotubule formation.[178] Several studies have suggested that Oxt could have a neuroprotective role in neurodegeneration, as it could promote anti-inflammation, reduce ROS generation, and diminish pro-inflammation cascades in microglia.[179–181] Such effects were also observed in the tMCAO stroke rat model.[182]

The interactions between Oxt and transition metal ions are an area of interest in bioinorganic chemistry.[152–154] The coordination of Oxt to divalent metal ions, including Mg(II), Ca(II), Mn(II), Ni(II), Co(II), Cu(II), and Zn(II), has been identified, as represented in Fig. 5d.[152] Bowers and coworkers reported two different binding modes of Cu(II) to Oxt by computational analysis (Fig. 5b).[152] Both modes include the primary amine at the N-terminus and two N donor atoms from the amide backbones between Pro7/Leu8 and Leu8/Gly9. A fourth ligand differs depending on the mode. It is either one N donor atom from the amide backbone between Asn5 and Cys6 or the amidated C-terminus.[152] Recent paramagnetic enhancement NMR studies reported another 4N coordination mode of Cu(II)(Oxt).[153] Hurevich and coworkers illustrated the coordination sphere in Oxt composed of the N-terminal primary amine and three N donor atoms from amide backbones, including one between Cys1 and Tyr2 and two consecutive (Fig. 5b).[153] The effect of Cu(II) complexation with Oxt on its receptor binding has not yet been fully elucidated, however. The disulfide bond in Oxt may be cleaved in the presence of ROS,[154] which can affect normal functions of cyclic peptides (*vide supra*).[37,72]

In the case of Zn(II), computational studies showed two types of coordination modes to Oxt composed of either six or five O donor atoms.[152] As depicted in Fig. 5b, the coordination sphere in a quasi-octahedral geometry contains the carbonyl group from the amidated C-terminus and the amide backbones between Tyr2/Ile3, Ile3/Gln4, Gln4/Asn5, Cys6/Pro7, and Leu8/Gly9.[152] Another Zn(II)-binding mode is in a quasi-trigonal bipyramidal structure with the 1N4O coordination: the N donor atom from the N-terminal primary amine and four O donor atoms from the carbonyl groups of the amidated C-terminus and the amide backbones between Cys1/Tyr2, Gln4/Asn5, and Cys6/Pro7.[152] Zn(II) binding of Oxt can align Ile3, Gln4, and Asn5 in the same plane, three of which are essential for the interaction with a hydrophobic pocket on Oxt receptors. Such conformational rigidity attributed to the complexation between Zn(II) and Oxt can facilitate the hormone–receptor binding.[152]

Conclusions and future perspective

Neurotransmitters are the fundamental building blocks of neuronal signaling pathways, which regulate the intricate homeostasis of our body system.[13,16–18] Their vital roles in maintaining normal physiological functions have been documented in the literature.[11–15] The binding of transition metal ions to neurotransmitters, however, can potentially disrupt their normal functions, thereby leading to the development of various neurodegenerative diseases, such as AD, PD, amyotrophic lateral sclerosis, and HD.[100,127,142,147,148,154] Nonetheless, some interactions between metal ions and neurotransmitters have been reported to ameliorate the processes associated with neurodegeneration.[100–102] In this review, we briefly introduce small molecule-based neurotransmitters and peptide-based neurotransmitters and summarize their metal-binding properties. Transition metal ions, such as Cu(I/II), Zn(II), and Fe(II/III), can directly or indirectly interfere with normal functions of neurotransmitters through multiple mechanisms, including coordination, conformational or structural changes, and ROS generation. It should be noted that other various metalloproteins exist in physiological systems exhibiting different functions,[11–15] which was not covered in this review.

Despite significant progress in understanding the pathology of neurodegenerative diseases, the precise interplay between transition metal ions and neurotransmitters remains unclear.[100,127,142,147,148,154] This highlights the urgent need for detailed investigations into the coordination chemistry of neurotransmitters. Such studies are expected to yield crucial insights into the influence of transition metal ions on the functions of neurotransmitters, thereby paving the way for the development of novel therapeutic strategies in the field of neurodegeneration. Thus, we anticipate that future research will focus on identifying new therapeutic targets and potential drug candidates against the inter-communication between transition metal ions and neurotransmitters.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government [NRF-2022R1A3B1077319 (M. H. L.)] and the 2023 Research Fund of the University of Seoul (J. H.).

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