Copper Transporters? Glutathione Reactivity of Products of Cu–Aβ Digestion by Neprilysin

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ABSTRACT: Aβ1–42 is the major subspecies of Aβ peptides characterized by avid Cu(II) binding via the ATCUN/NTS motif. It is thought to be produced in vivo proteolytically by neprilysin, but in vitro experiments in the presence of Cu(II) ions indicated preferable formation of C-terminally truncated ATCUN/NTS species including Cu13Aβ4–15, Cu14Aβ4–9 and also Cu13Aβ12–16 all with nearly femtomolar affinities at neutral pH. Such small complexes may serve as shuttles for copper clearance from extracellular brain spaces, on condition they could survive intracellular conditions upon crossing biological barriers. In order to ascertain such possibility, we studied the reactions of Cu13Aβ4–15, Cu14Aβ4–9, Cu13Aβ12–16, and Cu13Aβ1–16 with reduced glutathione (GSH) under aerobic and anaerobic conditions using absorption spectroscopy and mass spectrometry. We found Cu13Aβ4–16 and Cu14Aβ5–9 to be strongly resistant to reduction and concomitant formation of Cu(I)–GSH complexes, with reaction times ~10 h, while Cu13Aβ12–16 was reduced within minutes and Cu13Aβ1–16 within seconds of incubation. Upon GSH exhaustion by molecular oxygen, the Cu13Aβ complexes were reformed with no concomitant oxidative damage to peptides. These findings reinforce the concept of Aβ4–42 peptides as physiological trafficking partners of brain copper.

Aβ peptides are products of extracellular hydrolysis of amyloid precursor protein (APP) present in neuronal synaptic membranes. Overproduction or excessive aggregation of Aβ has been long implicated as an upstream cause of neuronal death in Alzheimer’s disease (AD). This concept gained recent reinforcement when direct deleterious action of Aβ dimers on neuronal glutamate receptors was demonstrated. Aβ peptides are a heterogeneous peptide family, generated by a number of primary (acting on APP) and secondary (acting on Aβ) proteases. The most studied members of the Aβ family are Aβ1–40 in health and Aβ1–42 in AD human brains. Aβ1–42, Aβ1–40, Aβ1–40, and Aβ1–42 peptide fragmentation was observed. The fast digestion of the Gh9–Tyr10 bond yielded the Cu13-complexed short peptide Aβ1–9. Additionally, a complex of Aβ12–16 was generated abundantly when Aβ1–16 was used as a substrate and was also present as a minor species for Aβ1–40. Aβ4–9 and Aβ12–16 are even stronger Cu13 chelators than Aβ1–16 with Kf of 6.6 mM and 9.5 mM vs 30 mM at pH 7.4. This finding gave rise to an idea that such complexes might serve as shuttles for removing excess copper from the brain.

Crossing the blood–brain barrier (BBB) is a complicated and not fully elucidated process, involving passage through the resting state of glutamatergic synapse, after the physiological Cu2+ release during neurotransmission. Digestion of Aβ peptides is considered as one of the major routes of their detoxification. They are thought to be cleaved down to oligopeptides that can cross the blood–brain barrier. An Aβ-specific peptidase has not been found. Instead, a number of brain proteases with other known functions have been implicated in this process, including neprilysin (NEP), angiotensinogen converting enzyme (ACE), and insulin degrading enzyme (IDE). NEP action on Aβ1–16 has also been indicated as the main source of Aβ4–42 in the brain. A recent study of Aβ1–16 and Aβ1–40 cleavage by NEP in the presence and absence of Cu13 ions did not quite reproduce such activity, however. Instead a significant extent of peptide fragmentation was observed. The fast digestion of the Gh9–Tyr10 bond yielded the Cu13-complexed short peptide Aβ1–9. Additionally, a complex of Aβ12–16 was generated abundantly when Aβ1–16 was used as a substrate and was also present as a minor species for Aβ1–40. Aβ4–9 and Aβ12–16 are even stronger Cu13 chelators than Aβ1–16 with Kf of 6.6 mM and 9.5 mM vs 30 mM at pH 7.4. This finding gave rise to an idea that such complexes might serve as shuttles for removing excess copper from the brain.

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Changes occurring in the course of reactions of CuII(Aβ4−16) allowed us to identify and assign the spectral roles in CuII transport in the brain. The diﬀerential kinetic resistance of the parent complex to such reaction.32 We therefore decided to follow the reaction of Aβ4−16 peptides with GSH in more detail, using Aβ4−16 as a suitable soluble, nonaggregating substitute of Aβ4−42. We also tested Aβk−9 and Aβk−12. Our experiments were performed under aerobic (21% O2) and anaerobic (<1% O2) conditions in order to gain insight into the relation of the studied reaction to oxidative stress conditions. The differential kinetic resistance of the studied complexes to reduction supports their possible roles in CuII transport in the brain.

In initial experiments, 0.315 mM CuII ions were reacted for 24 h with 1.75 mM GSH in 20 mM ammonium acetate buffer, pH 7.4, carried out for 25−30 h at 25 °C under aerobic (A) and anaerobic (B) conditions. UV−vis spectrum of CuII(Aβ4−16) showed by dashed line. The spectra were recorded in 10 min intervals. Insets show selected kinetic traces at 525 nm.

![Figure 1](https://dx.doi.org/10.1021/acs.inorgchem.0c00427)

**Figure 1.** UV−vis spectra of the reaction of 0.315 mM Cu(II) ions with 1.75 mM GSH in the presence of 0.35 mM Aβ4−16 in 20 mM ammonium acetate buffer, pH 7.4, carried out for 25−30 h at 25 °C under aerobic (A) and anaerobic (B) conditions. UV−vis spectrum of CuII(Aβ4−16) showed by dashed line. The spectra were recorded in 10 min intervals. Insets show selected kinetic traces at 525 nm.

### Table 1. Initial Reaction Velocities, V0, and Conversion Degrees of CuII Reduction to CuI/GSH in the Presence of Aβ4−16 Peptide

| Condition       | 18 °C  | 25 °C  | 37 °C  | 25 °C  |
|-----------------|-------|-------|-------|-------|
| V0 (10 M/s)     | 5.0 ± 0.2 | 10 ± 1 | 21 ± 3 | 9 ± 4 |
| Conversion degree | 0.58 ± 0.03 | 0.65 ± 0.04 | 0.64 ± 0.05 | 0.92 ± 0.03 |

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layer of epithelial cells forming the blood vessel wall.26 Therefore, the transferred molecule could be exposed for a certain amount of time to intracellular conditions, including millimolar (0.5−10 mM) concentrations of reduced glutathione (GSH).27 GSH is the main reducing agent for CuII species entering the cell interior and is also implicated in the intracellular Cu transport.28−30 It is also present extracellularly in the brain, serving as neuromodulator.31 GSH facilitated the otherwise very sluggish reductive copper transfer from Aβ4−16 to metallothionein-3 (MT-3), indicating that it could reduce the Aβk−12-bound Cu(II) to Cu(I) despite the electrochemical resistance of the parent complex to such reaction.32

This CuII reduction phase lasted for about 9 h and reproducibly reached about 65% CuII conversion at 25 °C, as calculated from the intensity of the CuII(Aβk−16) d−d band at 525 nm (Table 1). It was followed by the shorter reoxidation phase, which led to a practically full restoration of CuII(Aβk−16). In the absence of Aβk−16, the CuIIGSSG complex absorbing at 625 nm was the final reaction product (Figure S1). It was not formed in the presence of CuII(Aβk−16), because of the log K diﬀerence at pH 7.4 in favor of the latter, 10.37 vs 13.53.15,35 The reaction rates increased with temperature (Figure S5). The ESI-MS analysis of reaction products indicated the absence of covalent oxidative modification of Aβ4−16 (Figures S6 and S7). The only change in its mass spectrum was due to partial detachment of bound CuII ion resulting from its capture by GSH. The mass defect of 2 Da, seen only in the copper-containing species, indicated the native ATCUN/NTS complex with two deprotonated, CuII-bound amide nitrogens.15 A transient spectral feature at 390−405 nm accompanied the CuI reoxidation phase. The same feature was present during the reoxidation phase of CuII/GSH reaction in the absence of Aβ4−16 (Figure S8); hence it involves neither Aβk−16 nor its CuII complex. A similar band was seen previously in a study of CuII complexes in MT-3 and interpreted to originate from CuII−CuI interactions in the CuII-thiolate cluster.36 Indeed, CuI preferentially forms a CuII-thiolate cluster at the molar excess of GSH.35 However, the selective appearance of this low-energy band during oxidative decomposition of CuII(GSH) by molecular oxygen...
suggests a contribution from partially oxidized species such as disulfide or CuII. This issue will be investigated separately.

The next series of reduction experiments was performed under the effectively anaerobic conditions, and indeed only the reduction phase of the reaction was observed during the 24 h incubation, leading to full CuII reduction (Figure 1B). Upon extending the incubation to 50 h, however, the reoxidation phase was observed after about 36 h of the incubation (Figure S9). This effect was due to ambient oxygen penetration of the samples residing in the spectrophotometer. The comparison of kinetic traces indicated the similarity of the early phase of the reduction process between the aerobic and anaerobic conditions (Figure S10). These traces exhibited the mathematical form of first order kinetics for all conditions, only differing by the degree of CuII reduction: ca. 65% under aerobic and nearly 100% under anaerobic conditions. However, as the actual reaction order was not determined, we compared the kinetics of individual reactions using initial velocities. The rate of Cu(II) reduction did not depend on the presence of ambient oxygen (Tables 1 and 2).

Table 2. Initial Reaction Velocities, $V_0$, and Conversion Degrees of CuII Reduction to CuI/GSH Performed at 25 °C in the Presence of $\beta_{12-16}$ and $\beta_{14-9}$ Peptides

|        | aerobic | anaerobic |
|--------|---------|-----------|
| $V_0$  | $7 \pm 2$ | $10 \pm 2$ |
| conversion degree | $0.54 \pm 0.05$ | $0.91 \pm 0.04$ |
| $\beta_{12-16}$ | | |
| $V_0$  | $2200 \pm 500$ | $1600 \pm 400$ |
| conversion degree | $0.97 \pm 0.02$ | $0.98 \pm 0.02$ |

“Determined from the initial decay of the d–d band (527 and 524 nm, respectively). Velocities are given in nM/s; all data are shown ± SD.

Figure 2 presents examples of experiments performed aerobically with Cu(II) complexes of $\beta_{14-9}$ and $\beta_{12-16}$ peptides. The CuA$\beta_{14-9}$ reduction was similarly slow, but that of CuA$\beta_{12-16}$ was about 200 times faster than that of CuA$\beta_{14-9}$ (Table 2). The reoxidation phase occurred, however, similarly in all three cases (Figures 1 and 2). The reduction of CuA$\beta_{12-16}$ under the same conditions was too fast for quantitation (Figure S11). The kinetic, but not thermodynamic, resistance of CuA$\beta_{14-16}$ to reduction to CuI species by thiols has been indicated in previous experiments.32,37 Its kinetic character is reinforced by fast reduction of CuA$\beta_{12-16}$ which has higher thermodynamic stability than CuA$\beta_{14-16}$.25,26 A clue for the mechanistic basis of this behavior is provided by the accelerating role of glutamic acid in both reductive copper transfer to MT-3 and nonreductive transfer to EDTA, along the affinity gradient.38 This finding was interpreted in terms of assistance of copper transfer from the ATCUN/NTS motif via a putative partially coordinated intermediate species prone to form a ternary complex with a small transfer catalyst ligand. A similar mechanism was recently proposed in a study of Cu(II) reduction by GSH alone.39 In the case of CuA$\beta_{12-16}$ the fast CuII reduction is most likely facilitated by the His residue in position two of the peptide chain, able to provide an alternatively coordinated, minor 3N species.40,41 Such complexes are known to exchange CuII ions rapidly.42 They can also stabilize transient CuI species.38 CuA$\beta_{12-16}$ is known to facilitate CuII reduction to CuI by a number of mechanisms and is prone to ternary complex formation.43,44

Summarizing, the results presented above indicate that CuA$\beta_{12-16}$ and especially CuA$\beta_{14-9}$ are sufficiently kinetically resistant to reduction by physiological concentrations of GSH to survive in the cell cytosol for hours without eliciting oxidative damage, while CuA$\beta_{12-16}$ and CuA$\beta_{14-9}$ do not have this ability. Therefore, CuA$\beta_{12-16}$ complexes are good candidates to shuffle CuII across the blood–brain barrier and in and out of the brain cells.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.0c00427.

Experimental details, additional spectroscopic experiments, mass spectrometry data (PDF)

Figure 2. UV–vis spectra of the reaction of 0.315 mM Cu(II) ions with 1.75 mM GSH in the presence of 0.35 mM $\beta_{14-9}$ (A) and $\beta_{12-16}$ (B) in 20 mM ammonium acetate buffer, pH 7.4, carried out for 22–24 h at 25 °C under aerobic conditions. The spectra were recorded in 10 min intervals. Insets show selected kinetic traces at 527 nm (A) and 524 nm (B).
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Notes
The authors declare no competing financial interest.

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REFERENCES

(1) Selkoe, D. J. Amyloid β Protein Precursor and the Pathogenesis of Alzheimer’s Disease. Cell 1989, 58 (4), 611–612.
(2) Müller, U. C.; Deller, T.; Korte, M. Not Just Amyloid: Physiological Functions of the Amyloid Precursor Protein Family. Nat. Rev. Neurosci. 2017, 18 (5), 281–298.
(3) Selkoe, D. J. Alzheimer’s Disease: Genes, Proteins, and Therapy. Physiol. Rev. 2001, 81 (2), 741–766.
(4) Deshpande, A.; Mina, E.; Glabe, C.; Busciglio, J. Different Conformations of Amyloid Beta Induce Neurotoxicity by Distinct Mechanisms in Human Cortical Neurons. J. Neurosci. 2006, 26 (22), 6011–6018.
(5) Masters, C. L.; Selkoe, D. J. Biochemistry of Amyloid β-Protein and Amyloid Deposits in Alzheimer Disease. Cold Spring Harbor Perspect. Med. 2012, 2 (6), a006262.
(6) Zott, B.; Simon, M. M.; Hong, W.; Unger, F.; Chen-Engerer, H.-J.; Frosch, M. P.; Sakmann, B.; Walsh, D. M.; Konnerth, A. A Vicious Cycle of β Amyloid-Dependent Neuronal Hyperactivation. Science (Washington, DC, U.S.) 2019, 365 (6453), 559–565.
(7) Lewis, H.; Beher, D.; Cookson, N.; Oakley, A.; Piggott, M.; Morris, C. M.; Jaros, E.; Perry, R.; Ince, P.; Kenny, R. A.; Ballard, C. G.; Shearmur, M. S.; Kalaria, R. N. Quantification of Alzheimer Pathology in Ageing and Dementia: Age-Related Accumulation of Amyloid-Beta(42) Peptide in Vascular Dementia. Neuropathol. Appl. Neurobiol. 2006, 32 (2), 103–118.
(8) Portelius, E.; Bogdanovic, N.; Gustavsson, M. K.; Volkman, I.; Brinkmalm, G.; Zetterberg, H.; Winblad, B.; Blennow, K. Mass Spectrometric Characterization of Brain Amyloid Beta Isoform Signatures in Familial and Sporadic Alzheimer’s Disease. Acta Neuropathol. 2010, 120 (2), 185–193.
(9) Alies, B.; Renaglia, E.; Rózga, M.; Bal, W.; Fallar, P.; Hureau, C. Cu(II) Affinity for the Alzheimer’s Peptide: Tyrosine Fluorescence Studies Revisited. Anal. Chem. 2013, 85 (3), 1501–1508.
(10) Young, T. R.; Kirchner, A.; Wedd, A. G.; Xiao, Z. An Integrated Study of the Affinities of the Ap16 Peptide for Cu(I) and Cu(II): Implications for the Catalytic Production of Reactive Oxygen Species. Metallomics 2014, 6 (3), 505–517.
(11) Conte-Daban, A.; Baghehanshi, V.; Sayen, S.; Guillon, E.; Journaux, Y.; Gottard, G.; Linnard, L.; Hureau, C. Link between Affinity and Cu(II) Binding Sites to Amyloid-β Peptides Evaluated by a New Water-Soluble UV-Visible Ratiometric Dye with a Moderate Cu(II) Affinity. Anal. Chem. 2017, 89 (3), 2155–2162.
(12) Cheignon, C.; Jones, M.; Atrían-Blasco, E.; Kieffer, I.; Fallar, P.; Collin, F.; Hureau, C. Identification of Key Structural Features of the Elusive Cu–Aβ Complex That Generates ROS in Alzheimer’s Disease. Chem. Sci. 2017, 8 (7), 5107–5118.
(13) Cheignon, C.; Fallar, P.; Testemdale, D.; Hureau, C.; Collin, F. Metal-Catalyzed Oxidation of Aβ and the Resulting Reorganization of Cu Binding Sites Promote ROS Production. Metallomics 2016, 8 (10), 1081–1089.
(14) Cheignon, C.; Tomas, M.; Bonnefont-Rousselot, D.; Fallar, P.; Hureau, C.; Collin, F. Oxidative Stress and the Amyloid Beta Peptide in Alzheimer’s Disease. Redox Biol. 2018, 14, 450–464.
(15) Mital, M.; Wezynfeld, N. E.; Frączyk, T.; Wiloch, M. Z.; Wawrzyniak, U. E.; Bonna, A.; Tumpach, C.; Barnham, K. J.; Haigh, C. L.; Bal, W.; Drew, S. C. A Functional Role for Aβ in Metal Homeostasis? N-Truncation and High-Affinity Copper Binding. Angew. Chem., Int. Ed. 2015, 54 (36), 10460–10464.
(16) Harford, C.; Sarkar, A. B. Amino Terminal Cu(II)- and Ni(II)-Binding (ATCUN) Motif of Proteins and Peptides: Metal Binding, DNA Cleavage, and Other Properties. Acc. Chem. Res. 1997, 30 (3), 123–130.
(17) Stefaniak, E.; Bal, W. Binding Properties of N-Truncated Aβ Peptides: In Search of Biological Function. Inorg. Chem. 2019, 58 (20), 13561–13577.
(18) Hopt, A.; Korte, S.; Fink, H.; Panne, U.; Niessner, R.; Jahn, R.; Kretzschmar, H.; Herms, J. Methods for Studying Synaptosomal Copper Release. J. Neurosci. Methods 2003, 128 (1), 159–172.
(19) Shibata, M.; Yamada, S.; Kumar, S. R.; Calero, M.; Bading, J.; Frangione, B.; Holtzman, D. M.; Miller, C. A.; Strickland, D. K.; Ghiso, J.; Zlokovick, B. V. Clearance of Alzheimer’s Amyloid-S(1–40) Peptide from Brain by LDL Receptor-Related Protein-1 at the Blood-Brain Barrier. J. Clin. Invest. 2000, 106 (12), 1489–1499.
(20) Deane, R.; Du Yan, S.; Subramaray, R. K.; LaRue, B.; Jovanovic, S.; Hogg, E.; Welch, D.; Manness, L.; Lin, C.; Yu, J.; Zhu, H.; Ghiso, J.; Frangione, B.; Stern, A.; Schmidt, A. M.; Armstrong, D. L.; Arnold, B.; Lilienwik, B.; Nawroth, P.; Hofman, F.; Kindy, M.; Stern, D.; Zlokovick, B. RAGE Mediates Amyloid-β Peptide Transport across the Blood-Brain Barrier and Accumulation in Brain. Nat. Med. 2003, 9 (7), 907–913.
(21) Paroni, G.; Bisciglai, P.; Seripa, D. Understanding the Amyloid Hypothesis in Alzheimer’s Disease. J. Alzheimers Dis. 2019, 68 (2), 493–510.
(22) Kanemitsu, H.; Tomiyama, T.; Mori, H. Human Neprilysin Is Capable of Degrading Amyloid β Peptide Not Only in the Monomeric Form But Also the Pathological Oligomeric Form. Neurosci. Lett. 2003, 350 (2), 113–116.
(23) Oefner, C.; Roques, B. P.; Fournie-Zaluski, M.-C.; Dale, G. E. Structural Analysis of Neprilysin with Various Specific and Potent Inhibitors. Acta Crystallogr., Sect. D: Biol. Crystallogr. 2004, 60 (2), 392–396.
(24) Mital, M.; Bal, W.; Frączyk, T.; Drew, S. C. Interplay between Copper, Neprilysin, and N-Truncation of β-Amyloid. Inorg. Chem. 2018, 57 (11), 6193–6197.
(25) Bossak-Ahmad, K.; Mital, M.; Plonka, D.; Drew, S. C.; Bal, W. Oligopeptides Generated by Neprilysin Degradation of β-Amyloid Have the Highest Cu(II) Affinity in the Whole Aβ Family. Inorg. Chem. 2019, 58 (1), 932–943.

https://dx.doi.org/10.1021/acs.inorgchem.0c00427
Inorg. Chem. 2020, 59, 4186–4190
(26) Deane, R.; Bell, R. D.; Sagare, A.; Zlokovic, B. V. Clearance of Amyloid-Beta Peptide across the Blood-Brain Barrier: Implication for Therapies in Alzheimer’s Disease. CNS Neurol. Disord.: Drug Targets 2009, 8 (1), 16–30.
(27) Maher, P. The Effects of Stress and Aging on Glutathione Metabolism. Ageing Res. Rev. 2005, 4 (2), 288–314.
(28) Sies, H. Glutathione and Its Role in Cellular Functions. Free Radical Biol. Med. 1999, 27, 916.
(29) Hatori, Y.; Lutsenko, S. The Role of Copper Chaperone Atx1 in Coupling Redox Homeostasis to Intracellular Copper Distribution. Antioxidants 2016, 5 (3), 25.
(30) Maryon, E. B.; Molloy, S. A.; Kaplan, J. H. Cellular Glutathione Plays a Key Role in Copper Uptake Mediated by Human Copper Transporter 1. Am. J. Physiol. Cell Physiol. 2013, 304 (8), C768–C779.
(31) Bachhawat, A. K.; Thakur, A.; Kaur, J.; Zulkiфи, M. Glutathione Transporters. Biochim. Biophys. Acta, Gen. Subj. 2013, 1830 (5), 3154–3164.
(32) Santoro, A.; Ewa Wezynfeld, N.; Vašáč, M.; Bal, W.; Faller, P. Cysteine and Glutathione Trigger the Cu-Zn Swap between Cu(II)-Amyloid-B4–16 Peptide and Zn7-Metallothionein-3. Chem. Commun. 2017, 53 (85), 11634–11637.
(33) Morgan, M. T.; Nguyen, L. A. H.; Hancock, H. L.; Fahrni, C. J. Glutathione Limits Aquacopper(I) to Sub-Femtomolar Concentrations through Cooperative Assembly of a Tetranuclear Cluster. J. Biol. Chem. 2017, 292 (52), 21558–21567.
(34) Speisky, H.; Gómez, M.; Carrasco-Pozo, C.; Pastene, E.; Lopez-Alarcón, C.; Olea-Azar, C. Cu(I)-Glutathione Complex: A Potential Source of Superoxide Radicals Generation. Bioorg. Med. Chem. 2008, 16 (13), 6568–6574.
(35) Jánossy, K.; Súvágó, I.; Kozlowski, H. Transition Metal Complexes of Amino Acids and Derivatives Containing Disthophosphate Bridges. Inorg. Chem. Acta 1988, 151 (2), 117–123.
(36) Meloni, G.; Faller, P.; Vašáč, M. Redox Silencing of Copper in Metal-Linked Neurodegenerative Disorders: Reaction of Zn7Metallothionein-3 with Cu2+ Ions. J. Biol. Chem. 2007, 282 (22), 16068–16078.
(37) Wezynfeld, N. E.; Stefaniak, E.; Stachucy, K.; Drozd, A.; Ponka, D.; Drew, S. C.; Krężel, A.; Bal, W. Resistance of Cu(Ap4–16) to Copper Capture by Metallothionein-3 Supports a Function for the Ap4–42 Peptide as a Synthetic CuIIScavenger. Angew. Chem., Int. Ed. 2016, 55 (29), 8235–8238.
(38) Santoro, A.; Wezynfeld, N.; Stefaniak, E.; Pomorski, A.; Ponka, D.; Krężel, A.; Bal, W.; Faller, P. Cu Transfer from Amyloid-B4–16 to Metallothionein-3: The Role of Neurotransmitter Glutamate and Metallothionein-3 Zn(II)-Load States. Chem. Commun. 2018, 54, 12634–12637.
(39) Ngamchuea, K.; Batchelor-McAuley, C.; Compton, R. G. The Copper(II)-Catalyzed Oxidation of Glutathione. Chem. - Eur. J. 2016, 22 (44), 15937–15944.
(40) Gonzales, P.; Vileno, B.; Bossak, K.; El Khoury, Y.; Hellwig, P.; Bal, W.; Hureau, C.; Faller, P. CuII Binding to the Peptide Ala-His-His4-Chimera of the Canonical CuII-Binding Motifs Xxx-His and Xxc-Zxx-His. Inorg. Chem. 2017, 56 (24), 14870.
(41) Gonzales, P.; F. Bossak-Ahmad, K.; Vileno, B.; Wezynfeld, N. E.; El Khoury, Y.; Hellwig, P.; Hureau, C.; Bal, W.; Faller, P. Triggering Cu-Coordination Change in Cu(II)-Ala-His-His by External Ligands. Chem. Commun. 2019, 55 (56), 8110–8113.
(42) Hureau, C.; Eury, H.; Guillot, R.; Bijani, C.; Sayen, S.; Solari, P.-L.; Guillon, E.; Faller, P.; Dorlet, P. X-Ray and Solution Structures of CuIWHK and CuIWAHK Complexes: Influence on Their Redox Properties. Chem. - Eur. J. 2011, 17 (36), 10151–10160.
(43) Atria Blasco, E.; Del Barrio, M.; Faller, P.; Hureau, C. Ascorbate Oxidation by Cu(Amyloid-4) Complexes: Determination of the Intrinsic Rate as a Function of Alterations in the Peptide Sequence Revealing Key Residues for Reactive Oxygen Species Production. Anal. Chem. 2018, 90 (9), 5909–5915.
(44) Atria Blasco, E.; Gonzalez, P.; Santoro, A.; Alies, B.; Faller, P.; Hureau, C. Cu and Zn Coordination to Amyloid Peptides: From Fascinating Chemistry to Debated Pathological Relevance. Coord. Chem. Rev. 2018, 371, 38–55.