Biochemistry

Viewpoint

Cite This: Biochemistry 2020, 59, 15−17

pubs.acs.org/biochemistry

Synaptic Copper, Amyloid-β, and Neurotransmitters in Alzheimer's Disease

Eunju Nam,[†] Geewoo Nam,[‡,†] and Mi Hee Lim*[,†]

[†]Department of Chemistry, Korea Advanced Institute of Science and Technology (KAIST), Daejeon 34141, Republic of Korea

[‡]Department of Chemistry, Ulsan National Institute of Science and Technology (UNIST), Ulsan 44919, Republic of Korea

Alzheimer's disease (AD), the most common form of dementia, is characterized by neurodegeneration, memory loss, and cognitive impairment.[1a] Notably reduced levels of neurotransmitters (e.g., acetylcholine, amino acids, monoamines) leading to neurotransmission deficits are indicated to prompt the symptoms and progression of AD.[1a] Cholinergic deficit as a consequence of the insufficient acetylcholine levels in the AD-affected brain is strongly implicated in undermining the central nervous system and compromising the patient's ability to learn and recall information.[1a] In addition, the dyshomeostasis and miscompartmentalization of metal ions, which are involved in neurotransmission with modulatory implications (e.g., antagonistic effects on neurotransmitter receptors and influence on activating ion channels), represent a key pathological feature of AD.[1a] Association of neurotransmitters or metal ions with amyloid-β (Aβ), an aggregation-prone peptide formed through the amyloidogenic processing of amyloid precursor protein (APP) at the synaptic membrane, indicates the intertwined pathology of AD. Despite the significance of such research, however, information on the effects of interactions among metal ions, Aβ, and neurotransmitters on AD-associated neurodegeneration is limited due to (i) the heterogeneous and metastable nature of Aβ and (ii) the dynamic environment at the synapse.

In the brains of AD patients, highly concentrated metals (e.g., 0.4 mM Cu, 0.9 mM Fe, 1 mM Zn) are localized in senile plaques composed of Aβ aggregates.[1a] Furthermore, copper is reported to reach high micromolar concentrations at the synapse upon neuronal excitation,[1b] which suggests the potential interaction between copper and Aβ at the synaptic cleft. Ying et al. simulated Cu(I/II) binding to Aβ in an in vitro model of the synaptic environment with a firing frequency in the range of 1−100 Hz.[2] Using reaction-diffusion simulations, a model system used to indicate potential binding reactions under specific conditions, when synaptic concentrations of Cu(I/II) or Zn(II) and Aβ were mimicked (e.g., 30 μM of Cu, 300 μM of Zn, 3 nM of Aβ), the newly generated Cu(I)−Aβ and Cu(II)−Aβ accounted for ca. 27% and 9% of the total Aβ concentration, respectively.[2] On the other hand, Zn(II) exhibited a low propensity for Aβ with Zn(II)−Aβ reaching only a picomolar concentration at the end of reaction-diffusion simulations.[2]

Cu(I/II) coordination to Aβ occurs through the *N*-terminal and histidine amino acid residues (e.g., D1, A2, H6, H13, H14) with notable binding affinities [i.e., K_d (for Cu(I)−Aβ), 10^{-15}−10^{-8} M; K_d (for Cu(II)−Aβ), 10^{-11}−10^{-7} M].[1a] Direct interactions of Aβ with Cu(I/II) change the conformation and aggregation pathways of the peptide (e.g., formation and stabilization of toxic oligomeric species, facilitation of Aβ aggregation).[1a] In addition, redox-active copper bound to Aβ can produce reactive oxygen species (ROS), such as hydroxyl radicals, superoxide, hydrogen peroxide, via Fenton-like reactions, which leads to oxidative stress.[1a] Therefore, multiple studies have proposed the potential involvement of synaptic Cu(I/II)−Aβ complexes in neurodegeneration.

Cu(I/II)−Aβ is reported to act as a catalyst capable of oxidizing monoamine neurotransmitters, including dopamine, epinephrine, and serotonin (Figure 1A).[3] The catalytic efficiency (k_{cat}/K_m) of Cu(I/II)−$Aβ_{40}$ for oxidizing dopamine was determined to be 2.8 which is 85-fold higher than that of dopamine autoxidation.[3] Among various isoforms of Aβ, soluble $Aβ_{1-16}$ indicated the greatest catalytic activity toward the oxidation of dopamine, epinephrine, serotonin, and L-DOPA.[3] Monitoring the oxidation of these neurotransmitters in the presence of both Cu(I/II)−Aβ and H_2O_2 revealed a significant increase in the catalytic rate, suggesting that Cu(I/II)−Aβ and ROS, produced under pathological conditions, could affect the oxidation of these signaling molecules and consequently cause defective neurotransmission and neurodegeneration.[3] Conversely, Nam et al. suggested that the direct interactions between Cu(I/II)−Aβ and neurotransmitters could influence the aggregation behavior of Cu(I/II)-bound Aβ (Figure 1B).[4] For example, dopamine and its structural derivatives prompted the oxidation of both $Aβ_{1-40}$ and $Aβ_{1-42}$ in the presence of Cu(II). Such oxidation altered the aggregation pathways of Aβ showing (i) the generation of amorphous and conformationally compact Aβ species rather than fibrils produced during the on-pathway aggregation; (ii) the disassembly of preformed Aβ aggregates.[4] Detailed mechanistic studies confirmed that ROS generated through the oxidative transformation of dopamine could be responsible for Aβ oxidation.[4]

Moreover, direct interactions among Cu(I/II), Aβ, and neurotransmitters could modify the homeostasis of metal ions. In the AD-affected brain tissue, *N*-terminal truncated $Aβ_{4-42}$ is found to be a dominant isoform of Aβ.[5a] $Aβ_{4-x}$ peptides contain a Cu(II)-specific H_2N-*Xxx*-*Zzz*-His (ATCUN) motif, which exhibits higher binding affinity for Cu(II) (i.e., picomolar to femtomolar) than $Aβ_{1-x}$.[5a] Studies employing $Aβ_{4-16}$ and a neurotransmitter, glutamate, have identified the potential role of glutamate in the transfer of Cu(II) between Cu(II)−$Aβ_{4-16}$ and metallothionein-3 (MT-3), the protein responsible for the transport and storage of metal ions (Figure

Special Issue: Future of Biochemistry: The Asia-Pacific Issue

Received: August 28, 2019
Published: October 11, 2019

DOI: 10.1021/acs.biochem.9b00775
Biochemistry 2020, 59, 15−17

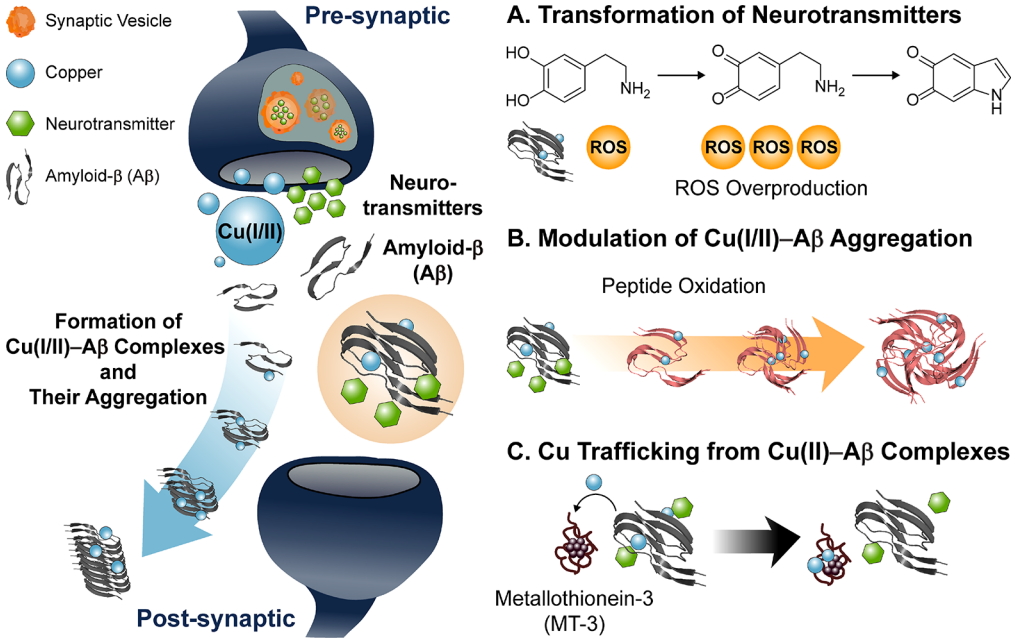

Figure 1. Potential interactions of Cu(I/II)−Aβ complexes with neurotransmitters at the synaptic cleft. Cu(I/II) secreted to the synaptic cleft upon neuronal excitation can be coordinated to extracellular Aβ peptides. Interactions between Cu(I/II)−Aβ complexes and neurotransmitters could affect (i) the oxidative transformation of neurotransmitters, (ii) the aggregation pathways of Cu(I/II)−Aβ, and (iii) the copper transport from Cu(II)−Aβ_{4-x} to MT-3 via formation of a transient ternary complex that is composed of Cu(II), Aβ_{4-x}, and a neurotransmitter.

1C).[5a] Although glutamate is a weak metal chelator, it was suggested at high concentrations (e.g., mM) during neurotransmission to shuttle Cu(II) from Aβ_{4-x} to Zn_7MT-3 by generating a transient ternary complex composed of Cu(II), Aβ_{4-x}, and glutamate.[5a] Such ternary complex formation may weaken copper binding to Aβ_{4-16} and thus assist in transferring copper from Cu(II)−Aβ_{4-16} to Zn_7MT-3.[5a] This indicates that intermolecular interactions among metal ions, Aβ, and neurotransmitters could be associated with metal trafficking at the synaptic cleft. Note that glutamate was reported at high concentrations to be a competitor for Cu(II) against Cu(II)−Aβ_{1-16} instead of forming a ternary complex, distinct from the interaction between Cu(II)−Aβ_{4-16} and glutamate.[5b]

In the midst of the complex and dynamic environment presented at the synaptic cleft, a potential interconnection among three elements, i.e., Cu(I/II), Aβ, and neurotransmitters, in the pathology of AD is proposed. Cu(I/II) and neurotransmitters released upon neuronal excitation are essential components in the synapse regulating the activation of neurotransmitter receptors and maintaining signal transduction. Under pathological conditions, Aβ is linked to neurodegeneration possibly through the interactions with these two components. These intercommunications toward the pathogenesis of AD could be possible based on multiple pathological features found in the AD-affected brain: (i) the dyshomeostasis and miscompartmentalization of metal ions; (ii) the deposition of Aβ aggregates; (iii) the deficient levels of neurotransmitters. Therefore, it is valuable to elucidate a molecular-level network among Cu(I/II), Aβ, and neurotransmitters, which can alter synaptic activities under pathophysiologically relevant conditions. Further studies investigating these aspects in detail would be worthwhile to identify the source of neurotoxicity at the synaptic cleft leading to AD.

AUTHOR INFORMATION

Corresponding Author

*E-mail: miheelim@kaist.ac.kr (M.H.L.).

ORCID

Mi Hee Lim: 0000-0003-3377-4996

Funding

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean government [NRF-2017R1A2B3002585 and NRF-2016R1A5A1009405 (to M.H.L.)]; KAIST (to M.H.L.).

Notes

The authors declare no competing financial interest.

REFERENCES

(1) (a) Savelieff, M. G., Nam, G., Kang, J., Lee, H. J., Lee, M., and Lim, M. H. (2019) Development of multifunctional molecules as potential therapeutic candidates for Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis in the last decade. *Chem. Rev. 119*, 1221−1322. (b) Kardos, J., Kovács, I., Hajós, F., Kálmán, M., and Simonyi, M. (1989) Nerve endings from rat brain tissue release copper upon depolarization. A possible role in regulating neuronal excitability. *Neurosci. Lett. 103*, 139−144.

(2) Branch, T., Barahona, M., Dodson, C. A., and Ying, L. (2017) Kinetic analysis reveals the identity of Aβ-metal complex responsible for the initial aggregation of Aβ in the synapse. *ACS Chem. Neurosci. 8*, 1970−1979.

(3) da Silva, G. F. Z., and Ming, L.-J. (2007) Metallo-ROS in Alzheimer's disease: Oxidation of neurotransmitters by Cu(II)−β-amyloid and neuropathology of the disease. *Angew. Chem., Int. Ed. 46*, 3337−3341.

(4) Nam, E., Derrick, J. S., Lee, S., Kang, J., Han, J., Lee, S. J. C., Chung, S. W., and Lim, M. H. (2018) Regulatory activities of dopamine and its derivatives toward metal-free and metal-induced amyloid-β aggregation, oxidative stress, and inflammation in Alzheimer's disease. *ACS Chem. Neurosci. 9*, 2655−2666.

(5) (a) Santoro, A., Wezynfeld, N. E., Stefaniak, E., Pomorski, A., Płonka, D., Krężel, A., Bal, W., and Faller, P. (2018) Cu transfer from

DOI: 10.1021/acs.biochem.9b00775
Biochemistry 2020, 59, 15−17

amyloid-β_{4-16} to metallothionein-3: the role of the neurotransmitter glutamate and metallothionein-3 Zn(II)-load states. *Chem. Commun. 54*, 12634−12637. (b) Frączyk, T., Zawisza, I. A., Goch, W., Stefaniak, E., Drew, S. C., and Bal, W. (2016) On the ability of CuAβ_{1-x} peptides to form ternary complexes: Neurotransmitter glutamate is a competitor while not a ternary partner. *J. Inorg. Biochem. 158*, 5−10.

DOI: 10.1021/acs.biochem.9b00775
Biochemistry 2020, 59, 15−17