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Challenges and Opportunities in Brain Bioinorganic Chemistry

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Abstract

Metal ions play critical roles in neurotransmission, memory formation, and sensory perception. Understanding the molecular details of these processes is the Holy Grail of metalloneurochemistry. Here we describe five challenges for collaborative teams of chemists, biologists, and neuroscientists to help make this dream a reality.

From its introduction into the chemical literature in 1978, the term holy grail has become a pervasive rhetorical device used to signify a momentous challenge facing the scientific community.^{1,2} In keeping with the expanse of chemistry as a discipline, many avenues of research have the potential to transform our understanding of a given subfield in a consequential way, and accordingly there are a multitude of holy grails worth pursuing. In this commentary, we present one such holy grail from the field of metalloneurochemistry:³ to understand the underlying bioinorganic chemistry behind brain function.

The brain is an organ of inordinate complexity and wonder. Thoughts, emotions—humanity itself—arise from carefully coordinated firings of neurons in ways that we are only beginning to appreciate. Propelled by advances in chemistry, genetics, nanotechnology, and microscopy, neuroscientists have made great progress elucidating biological pathways that allow ~85 billion neurons to transmit signals across 100 trillion synapses in the human brain.⁴ Efforts to expand this knowledge are likely to increase, especially given global initiatives to study neurophysiology and neurodegenerative disease.⁵ Success is predicated on the ability to connect the macro- and microscopic worlds, correlating behavior at the organismal level with biochemical mechanisms at the molecular level. Achieving this objective requires identification of the biochemical players and pathways that connect sensory input with signal transducers and, ultimately, the neural networks that comprise learning, memory, and function. Here, we discuss the importance of bioinorganic chemistry in these processes.

Ultimately, we would like to be able to explain how metal ions contribute to behavioral processes at the molecular level. Ca^{2+} is the best-studied metal ion in neurons and experiments to delineate the roles of Ca^{2+} ions are instructive models for exploring the behavior of others.^{6,7} Consider the role of Ca^{2+} in memory and learning. As depicted in Figure 1, when a mouse learns to navigate a Morris water maze, memory reconsolidation occurs in the hippocampus after Ca^{2+} influx into postsynaptic neurons triggers a variety of

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downstream events associated with long-term potentiation, including signaling cascades mediated by the Ca^{2+} -binding protein calmodulin (CaM).^{8,9} Structural biology and molecular biophysics have provided snapshots and dynamics revealing many details of these processes, including the coordination geometry of Ca^{2+} binding to CaM and architectural features of ion channels that admit and transport Ca^{2+} over other ions, including Mg^{2+} , Na^{+} and K^{+} .^{10,11} Exploration of the corresponding bioinorganic chemistry for all the metal ions in the brain remains fertile ground for exploration. Because the scope of the subject is broad, we focus on five achievable, if ambitious, goals for delineating the many roles of metal ions in the nervous system.

Goal 1

Determine the speciation, concentration, and distribution of metal ions in neural tissue. In order to understand fully the complicated bioinorganic chemistry of the brain, chemists need to identify metal ions that underlie the physiology and pathology of the nervous system. Included are ions that are tightly bound to biopolymers or small molecules, as well as those liberated ions that participate in signal transduction events. Mobile calcium, magnesium, sodium, potassium, iron, copper, and zinc ions all play such functional roles in neural activity. On the other hand, accumulation of metals such as mercury, lead, cobalt, chromium, and platinum, can evoke debilitating neuropathies. One of the first tasks is to develop tools to detect and characterize metal ions in neural tissue with high sensitivity. Of interest is the locale of these ions, which can migrate from subcellular compartments such as vesicles to larger synaptic circuitry throughout the brain. To help achieve this goal, sensors that provide the concentration of a specific analyte in live animals with high spatial and temporal resolution are particularly valuable. With such constructs in hand, investigators can turn their attention to solving specific biological problems. If, when addressing the important questions in neuroscience, the need arises to develop new sensor molecules, next generation probes can be synthesized for the task. In this manner, novel and important contributions to both sensor design and metalloneurochemical fields can be made. Interdisciplinary collaboration with other scientists is essential for this undertaking.

The concentration and spatial distribution of metal ions in the brain change over the course of a lifetime, with important consequences for proper development in youth and for stemming the progression of neurodegeneration during old age. Although metal ions have been implicated in a number of processes related to neural segregation and differentiation during development, more studies are needed to identify the relevant biochemical pathways that are activated or suppressed. Determining the role of metals in the etiology of neurodegenerative diseases, such as amyotrophic lateral sclerosis or Huntington's, is also an area of importance.¹² Methodologies to globally monitor metal ion homeostasis are required to understand the physiological origin and neurological impact of these changes. Methods for preparing high quality maps delineating metal ion localization over long periods of time are especially desirable.

Goal 2

Understand the chemistry underlying the control of synaptic metal ion concentrations. During neurotransmission, synapses are flooded with Ca^{2+} , Na^+ , K^+ , and other metal ions on the millisecond timescale, and local concentrations can increase by orders of magnitude.⁶ Efficient efflux is required to reset the system for subsequent signaling events. Although details about the disposition of Ca^{2+} have been elucidated,⁶ clearance mechanisms for other metal ions, such as Zn^{2+} , are not understood. Methods for simultaneously determining intra- and extracellular metal ion concentrations at sub-millisecond temporal resolution are required for exploring fundamental signaling events in real time. Of interest are the dissociation of metal ions from synaptic proteins and the processes by which neurons recycle the ions and distribute them to adjacent presynaptic, postsynaptic, and glial cells.

Goal 3

Delineate chemical details of pathways that control metal ion homeostasis beyond synapses. It is important to identify pathways that govern metal ion homeostasis in neurons and to explore the clinical implications of functional impairment, such as those relevant to bipolar disorders, schizophrenia, dementia, ischemic stroke, traumatic brain injury, or seizures. Investigators must devise and apply tools to study these systems and answer specific questions about the regulation of global metal ion homeostasis in the brain such as (1) How does oxidative stress contribute to metal ion dysregulation? (2) Do metal-dependent transcription factors cause a loss of active proteins or turn-on otherwise silent genes? (3) Which transporters control compartmentalization into organelles? Research in this area should also focus on macromolecular coordination chemistry that gives rise to the metal ion selectivity of transporters and other biomolecules that are essential for maintaining cellular homeostasis.

Goal 4

Understand how metal ions regulate sensory perception. Mounting evidence suggests that metals ions, particularly Zn^{2+} , play crucial roles in olfaction, audition, and somatosensory perception. In these systems, Zn^{2+} ions are co-released with glutamate into the synapse where they alter the activity of neuronal receptors, such as NMDA and AMPA receptors, in such a way as to attenuate or potentiate the synaptic response, thus providing another level of control over signal transduction.¹³⁻¹⁵ Many questions about the details of these systems remain unanswered, including how different metal ions interact or compete with each other to affect synaptic proteins. To determine how metal ions contribute to signal discrimination, propagation, and amplification, it will be necessary to develop a systems biology approach for deconvoluting metal ion interdependency and cooperativity. With the emergence of techniques to measure brain activity in live organisms, as revealed by fluorescent Ca^{2+} sensors, for example, it is possible to study the effects of controlled perturbations to metal ion homeostasis on neurotransmission.^{16,17} Because these techniques can be applied to diverse model systems ranging from zebrafish to mice, behavioral experiments can be designed to investigate sensory perception using a variety of platforms. For example, wildtype and mutant animals can be trained to react to a stimulus and then challenged by

application of metal chelators or exogenous metals directly to the intact brain to determine the effect of a given ion on behavior.

Goal 5

Apply the insights gleaned from these experiments to treat metal-associated pathologies. New therapeutic strategies to combat metal-mediated neurodegeneration are desperately needed and would improve the quality of life for millions of people.¹² The management of diseases arising from impaired metal ion homeostasis is a worthy pursuit, the attainment of which could benefit substantially from a better understanding of metal ion dynamics in the brain. In addition to devising treatments for diseases related to dysregulation of metal ion homeostasis, attention should be paid to disorders arising from abiological metals introduced into the nervous system. Clinical strategies for improving the outcome of children afflicted with lead poisoning and for ameliorating the side effects of metallothiopythetics currently used in the clinic, such as platinum anticancer drugs, some of which are dose-limited by the resulting polyneuropathies,¹⁸ are examples of pressing needs.

Much hard work remains to be done, but the rewards will be worthwhile. This exciting adventure has already begun and is surely not for the faint-of-heart, but for all others, as the voices cheered Sir Galahad on his quest for the Grail: "Ride on! the prize is near."¹⁹

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References

1. Halford B. A Crusade Against Holy Grails. *Chem Eng News*. 2009; 87:34.
2. Lippard SJ. Platinum Complexes: Probes of Polynucleotide Structure and Antitumor Drugs. *Acc Chem Res*. 1978; 11:211–217.
3. Burdette SC, Lippard SJ. Meeting of the minds: Metalloneurochemistry. *Proc Natl Acad Sci USA*. 2003; 100:3605–3610. [PubMed: 12655069]
4. Alivisatos AP, Andrews AM, Boyden ES, Chun M, Church GM, Deisseroth K, Donoghue JP, Fraser SE, Lippincott-Schwartz J, Looger LL, Masmanidis S, McEuen PL, Nurmikko AV, Park H, Peterka DS, Reid C, Roukes ML, Scherer A, Schnitzer M, Sejnowski TJ, Shepard KL, Tsao D, Turrigiano G, Weiss PS, Xu C, Yuste R, Zhuang X. Nanotools for Neuroscience and Brain Activity Mapping. *ACS Nano*. 2013; 7:1850–1866. [PubMed: 23514423]
5. Grillner S, Ip N, Koch C, Koroshetz W, Okano H, Polachek M, Poo M-m, Sejnowski TJ. Worldwide initiatives to advance brain research. *Nat Neurosci*. 2016; 19:1118–1122. [PubMed: 27571190]
6. Clapham DE. Calcium Signaling. *Cell*. 2007; 131:1047–1058. [PubMed: 18083096]
7. Palmer AE, Tsien RY. Measuring calcium signaling using genetically targetable fluorescent indicators. *Nat Protoc*. 2006; 1:1057–1065. [PubMed: 17406387]
8. Silva A, Paylor R, Wehner J, Tonegawa S. Impaired Spatial Learning in α -Calcium-Calmodulin Kinase II Mutant Mice. *Science*. 1992; 257:206–211. [PubMed: 1321493]
9. Kandel, ER., Schwartz, JH., Jessell, TM., Siegelbaum, SA., Hudspeth, AJ. *Principles of Neural Science*. 5th. McGraw-Hill; New York: p. 2013
10. Tang L, Gamal El-Din TM, Payandeh J, Martinez GQ, Heard TM, Scheuer T, Zheng N, Catterall WA. Structural basis for Ca^{2+} selectivity of a voltage-gated calcium channel. *Nature*. 2014; 505:56–61. [PubMed: 24270805]

11. Lippard, SJ., Berg, JM. Principles of Bioinorganic Chemistry. University Science Books; Mill Valley, CA: 1994.
12. Barnham KJ, Bush AI. Biological metals and metal-targeting compounds in major neurodegenerative diseases. *Chem Soc Rev.* 2014; 43:6727–6749. [PubMed: 25099276]
13. Paoletti P, Vergnano AM, Barbour B, Casado M. Zinc at glutamatergic synapses. *Neuroscience.* 2009; 158:126–36. [PubMed: 18353558]
14. Kalappa BI, Anderson CT, Goldberg JM, Lippard SJ, Tzounopoulos T. AMPA receptor inhibition by synaptically released zinc. *Proc Natl Acad Sci USA.* 2015; 112:15749–15754. [PubMed: 26647187]
15. Romero-Hernandez A, Simorowski N, Karakas E, Furukawa H. Molecular Basis for Subtype Specificity and High-Affinity Zinc Inhibition in the GluN1-GluN2A NMDA Receptor Amino-Terminal Domain. *Neuron.* 2016; 92:1324–1336. [PubMed: 27916457]
16. Dombeck DA, Khabbazi AN, Collman F, Adelman TL, Tank DW. Imaging Large-Scale Neural Activity with Cellular Resolution in Awake, Mobile Mice. *Neuron.* 2007; 56:43–57. [PubMed: 17920014]
17. Dana H, Mohar B, Sun Y, Narayan S, Gordus A, Hasseman JP, Tsegaye G, Holt GT, Hu A, Walpita D, Patel R, Macklin JJ, Bargmann CI, Ahrens MB, Schreier ER, Jayaraman V, Looger LL, Svoboda K, Kim DS. Sensitive red protein calcium indicators for imaging neural activity. *eLife.* 2016; 5:e12727. [PubMed: 27011354]
18. Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst.* 2008; 13:27–46. [PubMed: 18346229]
19. Tennyson, AT., Ricks, C. The poems of Tennyson in three volumes. Longman; Harlow, Essex: 1987.

Figure 1.

A reductionist view of Ca^{2+} in the brain linking behavior to underlying coordination chemistry. Morris water maze tests can be used to demonstrate spatial learning in wildtype and mutant mice. Learning is facilitated by Ca^{2+} -triggered signaling pathways relevant to long-term potentiation, including those governed by protein kinase C (PKC) and calmodulin (CaM, PDB 1CLL), which in turn activate (i) adenylyl cyclase (AC) to produce cAMP, which turns on protein kinase A (PKA); (ii) Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII), which phosphorylates AMPA receptors (AMPA); and (iii) nitric oxide synthase (NOS), which produces the putative retrograde signaling agent NO, among others.⁹