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Title

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Journal

Accounts of chemical research, 50(3)

ISSN

0001-4842

Author

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Publication Date

2017-03-01

DOI

10.1021/acs.accounts.6b00531

Peer reviewed

Bioinorganic Life and Neural Activity: Toward a Chemistry of Consciousness?

Published as part of the *Accounts of Chemical Research* special issue “Holy Grails in Chemistry”.

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ABSTRACT: Identifying what elements are required for neural activity as potential path toward consciousness, which represents life with the state or quality of awareness, is a “Holy Grail” of chemistry. As life itself arises from coordinated interactions between elements across the periodic table, the majority of which are metals, new approaches for analysis, binding, and control of these primary chemical entities can help enrich our understanding of inorganic chemistry in living systems in a context that is both universal and personal.

The traditionally narrow definitions of organic chemistry pertaining to living systems and inorganic chemistry to nonliving ones ignores the fact that virtually all of the elements on the periodic table of life are noncarbon. Indeed, from the water that spans over 70% of the planet and makes up 60% of our bodies¹ to the nitrogen and oxygen that encompasses 98% of our atmosphere to drive our food production for respiration² to the palette of mineral nutrients required to sustain all living organisms across all ecosystems,³ inorganic chemistry is central to our shared existence on this planet.

From this perspective, the periodic table represents an alphabet or set of basic characters or symbols for more complex forms of communication in living systems. Like translating and understanding any language, these elements alone represent the individual letter or character starting points that form words, leading to sentences to paragraphs to stories that give rise to higher-order expressions and thoughts. In this context, chemistry has the capacity not only to read these stories at the atomic and molecular level of letters and characters but to synthesize new, living language through arranging and rearranging the bonds between these atomic and molecular units to create something that is more than the sum of the individual parts. At the heart of this endeavor is studying the key elements and their speciations and molecular combinations that make the chemical language of life possible.

Against this backdrop, arguably the highest form of life is consciousness, where a living being has awareness of something within oneself or an external object. This experience is shared and universal, yet at the same time personalized to each individual. A potential path to understanding the abstract concept of consciousness in a more tangible way is to study the neural activity of the brain, which takes in everything we see, hear, smell, taste, and touch and then processes everything we learn and remember and everything we feel and forget (Figure 1). It is no coincidence that this unique biology is underpinned by unique chemistry, where this organ accumulates more

elements at higher concentrations than any other part of the body.^{4–6} For example, redox metals like copper and iron are particularly important owing to the high metabolic and signaling load of brain tissue, representing just 2% of body weight but 20% of body oxygen consumption.^{4,7} As such, the bioinorganic chemistry of the brain offers a rich area for discovery in the broadest of terms, and studying the contributions of metals to neural activity as a first step to finding the elusive chemistry of consciousness is the subject of this “Holy Grail” Commentary (Figure 1). Of particular interest is bioinorganic chemistry beyond active sites, where redox metals like copper are not only static metabolic cofactors at the center of enzymatic activity but can also serve as dynamic signals that bind and regulate protein function at external allosteric sites.^{8,9} This emerging field complements the well-recognized roles of redox-inactive elements like calcium, zinc, potassium, and sodium as brain signals.^{4–6}

Keeping with the analogy of the periodic table representing a chemical alphabet for the language of life, I propose a set of “ABCs” to illustrate progress and opportunities for learning about the chemistry of consciousness, which helps frame this quest for studying and shaping inorganic chemistry in living systems. I emphasize that such chemical tools and tactics can be more widely used to discover molecular-level phenomena in the world around us. My hope is that this discussion stimulates further activity in this frontier area of chemistry and captures the interests of a broader community.

■ ANALYSIS

As a starting point, being armed with the basic information on what elements exist in brain tissue leads to a series of fundamental questions. Where are they located? What is their

Received: October 21, 2016

Published: March 21, 2017

Figure 1. The brain is the center of consciousness that is underpinned by unique chemistry, including a high requirement for metals. The opportunity to uncover new roles for metals in biology has led to the emerging paradigm of transition metal signaling, where redox-active metals like copper and iron can not only serve in their traditional roles as static metabolic cofactors, but also be utilized in dynamic, kinetically labile forms that reversibly bind to cellular targets and influence their behavior. This bioinorganic frontier represents a Holy Grail of chemistry.

speciation? Which pools are static or dynamic? And how do they interact with each other? To accomplish this long-term goal, new analytical methods are needed. In this context, metals provide both unique challenges and opportunities for detection and analysis. They can neither be created nor destroyed under ambient biological conditions, making them attractive chemical signatures that have the potential to be tracked in an unambiguous way with spatial and temporal fidelity. At the same time, however, metals form coordination bonds that possess varying degrees of ionic and covalent character over a wide range of stability constants, which gives rise to a complex continuum between tightly bound, static metal pools used primarily for metabolism and loosely bound, labile ones exploited for signaling (Figure 1). Coupled with their inherent geometric as well as oxidation- and spin-state diversity, metals offer a rich area for further exploration at many different chemical levels. Direct imaging of total metal pools at various length scales using an emerging toolbox of techniques, including laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS), secondary ionization mass spectrometry (SIMS), and X-ray fluorescence microscopy (XFM),¹⁰ along with small-molecule and macromolecule imaging probes for metal ions that provide information on loosely bound, labile metal pools,^{9,11–13} can be used in concert to provide a coherent picture of metal homeostasis. The ability to target specific cell populations or tissue as well as subcellular structures will enable further advances with such imaging and analysis tools. Finally, another particular challenge is to determine metal speciation in live tissue, owing to the existence of both labile and static metal pools¹⁴ and the need to handle heterogeneous specimens to maintain the integrity of these stores.

BINDING

In addition to spatial and temporal analysis of distributions and concentrations of the bioinorganic elements in their native settings, a parallel avenue of inquiry for understanding metals in the brain is characterizing their synergistic bonding interactions, particularly spanning the time scales that encompass both faster signaling and slower metabolism processes. Indeed, metals pervade all aspects of the central dogma of biology, as they are required for function of all DNA and RNA molecules and approximately half of all proteins.¹⁵ In addition, they are involved in the synthesis and processing of many other lipids,

sugars, and other metabolites, including neurotransmitters like dopamine, norepinephrine, and glutamate and second messengers like cAMP.¹⁶ However, despite the ubiquitous need for and use of metals in biology, we are still in the earliest of stages with regard to discovery and study of new metal-binding units, particularly from a predictive identification of cryptic metal-dependent motifs beyond standard metalloprotein and metal–nucleic acid active sites. Advances in metalloproteomics technologies, including new metal-based affinity reagents and supports and chemoproteomic activity- and reactivity-based protein profiling methods, along with bioinformatics approaches specifically dedicated to metals, can be coupled to more in-depth biochemical characterization to identify new functional metal sites in living systems in solution as well as at the cell, tissue, and whole organism level.

CONTROL

With analytical data establishing the existence of particular metal sources in a given place at a given time in a given concentration, along with information on binding of these metals to specific molecular targets, a third area of investigation is external control of metal pools and interactions for tool platforms as well as for translational therapeutic applications. Metal supplements and metal chelators have long been used to treat global conditions of metal deficiency or excess, respectively, but as our understanding of metal homeostasis becomes more sophisticated, growing interest in the field of metal-attenuating compounds has emerged to regulate metal pools with greater spatial and temporal precision.¹⁷ Included are chelators with improved metal selectivity and an increased range of binding affinities, as well as ionophores that can redistribute metals across internal and external cellular membranes. In addition, caged probes activated by light, enzyme activity, reactive oxygen species, or various other chemical and biochemical stimuli can also enable spatial and temporal control of metal pools in a variety of biological settings.¹⁸ The combination of small-molecule and protein-based molecular imaging probes,^{19,20} along with selective chelators²¹ and caged compounds,²² have revolutionized the study of calcium in biology, particularly in neural systems, leaving a diverse array of possibilities to develop new technologies for other metals of importance to neuroscience and other biomedical and environmental applications. Indeed,

Figure 2. Models of transition metal signaling, as illustrated with representative examples from studies of copper. (a) Copper is a dynamic brain signal that moves in an activity-dependent manner in neurons, with further characterization showing that copper fluxes are essential for maintaining normal spontaneous activity, a fundamental property of all neural circuits. Labile copper pools can be probed using synthetic fluorescent indicators. (b) Copper is a natural regulator of lipolysis, the breakdown of fat, which is a central process in maintaining weight and energy stores in the body. Copper promotes lipolysis via the second messenger cAMP by inhibiting PDE3B, an enzyme responsible for its degradation. Biochemical studies establish a key reversible copper–cysteine interaction responsible for controlling lipolytic fluxes, linking transition metal and redox signaling pathways.

calcium imaging has emerged as one of the standard measures of neural activity across a variety of cell, tissue, and animal models, and copper, zinc, and iron imaging in particular are poised to provide complementary and unique information on specific neural circuits. Finally, researchers with interests in drug discovery should give increased attention to bioinorganic targets in the context of small molecules and biologics that can inhibit or activate metal-binding sites. This area of metals in medicine is ripe for exploration, particularly in the context of neuropathology owing to the high intrinsic need for metals in the brain.

■ COPPER SIGNALING IN THE BRAIN AND BEYOND

The foregoing discussion shows that transition metals offer a nexus between signaling and metabolism, and in this context, I have introduced the term transition metal signaling, which is defined as transition metal–biomolecule interactions that govern and coordinate biological activities in response to a stimulus.⁸ Our laboratory has identified this new paradigm for metals in biology through the discovery and study of redox-metal signaling, using copper as a first example (Figure 1). This work has embraced a diverse range of approaches, including multimodal metal imaging using chemical probes for molecular imaging of labile metal pools coupled with direct metal imaging techniques for assaying total metal pools, metalloproteomics and metallobiochemistry to identify and characterize new targets for transition metals, as well as metal-specific chelators and ionophores to probe and perturb physiology and pathology relevant to metal homeostasis.

Long-term efforts in our laboratory have focused on fundamental development of a toolbox of fluorescent and related imaging probes for monitoring labile copper pools, particularly in the Cu(I) state that is prevalent within the reducing environment of cells.^{23–25} As there is no one-size-fits-all technology to achieve this challenging goal because of the inherent diversity of biological systems, the hand-in-hand chemical development, characterization, and iteration of probes with direct biological evaluation must be pursued for each given

situation and an open spirit of collaboration and sharing between chemists and biologists can help meet this gap.^{23,26} A foundational discovery from these efforts was the direct observation of dynamic copper movements in stimulated neurons (Figure 2a), showing that redox transition metals are capable of fast fluxes that had been previously thought to be restricted to alkali and alkaline earth metals like sodium, potassium, and calcium. Neuronal depolarization triggers movement of copper from internal cell bodies to outer dendritic processes at synapses, as monitored using a combination of XFM supported by pilot studies with a third-generation fluorescent copper probe (Figure 2a, right).²⁷ The copper fluxes are dependent both on neural activity as well as intracellular calcium release, at a seconds to minutes time scale that is commensurate with signaling. Further studies in tissue and mouse models, aided by development of next-generation fluorescent copper reporters that enable labile copper imaging by one- and two-photon microscopy, establish that copper is essential for regulating spontaneous activity, a fundamental property of all neural circuits.²⁸ We further identified Ctr1 as a key target for this action, suggesting the possibility of transition metal-selective pores that could serve as dynamic gatekeepers for regulating signaling akin to ion channels for alkali and alkaline earth metals. Current efforts in the neurobiology of copper signaling include more basic mechanistic studies to define additional sources and targets of copper regulation, as well as translating this fundamental knowledge of copper dynamics to behavior and neurophysiology and its dysregulation in neurological and neurodegenerative disease. A recent report describing the roles of copper in regulating the OR2T11 odorant receptor to thiols demonstrates that this metal can contribute not only to neurotransmission but also to the earliest stages of sensory perception.²⁹

More recent results have expanded the concept of transition metal signaling with copper beyond the brain to peripheral tissue systems, presaging the broader use of these elements in a more diverse array of signaling contexts. In one example, we recently identified an essential role for copper in regulating

lipolysis, the breakdown of fat, which is a major metabolic process that controls body weight and energy stores (Figure 2b). Copper regulates lipolysis at the level of the second messenger cAMP, by altering the activity of the cAMP-degrading enzyme phosphodiesterase 3B (PDE3B).³⁰ Further biochemical studies reveal a key copper–cysteine interaction that lies outside the active site as the molecular origin for reversible copper-dependent inhibition of the enzyme, linking transition metal and redox signaling and motivating further investigation.

CONCLUDING REMARKS

The study of metals in neural activity and its connected systems is a Holy Grail along the larger quest for a true understanding of the elusive chemistry of consciousness. Indeed, metals play an essential yet insufficiently elucidated set of roles in signaling and metabolism as the primary letters and characters for building up the language of how we become aware and interact with ourselves and the world around us, and we must pursue fundamental learning of our basic ABCs in the relative infant stage of this emerging metals field. The molecular atlas that emerges from these bioinorganic elements will provide a living legacy that surely will lead to an appreciation for life that is greater than the individual chemical parts.

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Notes

The author declares no competing financial interest.

ACKNOWLEDGMENTS

I am an Investigator with the Howard Hughes Medical Institute and thank HHMI as well as NIH GM 79465 and DOE (LBNL Grant 101528-002) for research funding in support for our passion to study metals at the chemistry/biology interface.

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