The Future of Monitoring Molecules

The "monitoring molecules" community has its roots in a small but committed group of primarily chemists-turned-neuroscientists, as recollected by Mark Wightman.[1] From its inception, the field has largely comprised practitioners of two in vivo methods—microdialysis and voltammetry. Much of the early history of in vivo neurochemistry involved adapting and improving these methods. There was also friendly crossfire between groups using these different methods largely due to their complementary yet somewhat orthogonal strengths and weaknesses. Today, we are witnessing the power of each method when carried out in behaving animals. Chemical neurotransmission is being monitored so as to elucidate the roles of neurotransmitters, particularly dopamine and acetylcholine, in the control of complex behavior.

This special issue of *ACS Chemical Neuroscience* arises from the Monitoring Molecules in Neuroscience 15th International Conference held at the University of California, Los Angeles August 3−7, 2014 (http://www.monitoringmolecules.org/2014/). The meeting was dedicated to showcasing and discussing the strengths of current research on chemical neurotransmission. However, this collection of Viewpoints, Reviews, Letters, and Articles goes further insofar as many of its contributions seek to map the future of this field. As such, we require a broader definition of what it means to monitor molecules in neuroscience with the future largely characterized by three intermingled directions.

■ RESOLUTION

Increasing spatial, temporal, and chemical resolution is an overarching theme when it comes to current and future efforts in monitoring neurochemicals, particularly in the context of the U.S. BRAIN Initiative.[2] However, as Martin Sarter and Youngsoo Kim opine, there is key conceptual information to be gained by bridging existing intermediate spatial and temporal scales.[3] Rectifying findings from voltammetric recordings with those from microdialysis measurements has the potential to yield new and unifying insights into how behaviorally relevant information is encoded in chemical architectures. Moreover, mitigating inflammatory responses associated with implanting larger devices including microdialysis probes or multisite electrophysiological recording electrodes appears to improve the quality of data collected during acute and long-term recordings.

■ DIVERSIFICATION

A second trend is toward expanding the numbers and types of neurotransmitters included in measurement repertoires. Multiplexed and multimodal strategies, even in humans, are the goals. In addition to "classical" small-molecule neurotransmitters, a number of groups are focused on investigating the dynamics of neuropeptide signaling—en masse, in some cases. Another approach is to merge neurochemical and electrophysiological recordings using the same electrode or in the context of multisite electrodes. The spatial and molecular diversities of these approaches are anticipated to enable decoding information processing from single cells to circuits.

■ GENETICS

Chemical neurotransmission has been largely investigated via stimulated release using high extracellular K^+ with microdialysis or in response to electrical stimulation with voltammetric approaches. However, as resolution has improved across all scales and limits of detection have improved, investigators have recorded endogenous changes in neurotransmitter release (and reuptake) during the performance of complex behavioral tasks. This has enabled hypotheses about the involvement of neurotransmitters in specific circuits to be tested. As discussed by Kate Wassum and Paul Phillips, nowhere has this been more deeply investigated than with respect to motivated behavior and decision-making.[4] Increasingly sophisticated behavior paradigms and chronic recordings will be key to continued advancement in this area of research.

A further aspect of resolution involves how the diversity of brain neurons is differentiated. Two critical advances that greatly enhance control of neural activity—optogenetics and designer receptors exclusively activated by designer drugs (DREADDs)—are beginning to be combined with state-of-the-art in vivo molecular monitoring. Both enable the activity of specific genetically defined populations of neurons to be activated or repressed but with different time scales and mechanisms. As we move forward with tour de force combinations of technologies, a wider variety of neural circuits and neurotransmitters will be linked causally with diverse behaviors. Nonetheless, as delineated by Yong Ku Cho, it will be important to refine strategies for identifying interconnected neurons to include improved genetic resolution and integration with functional information.[5]

Genetically encoded neurotransmitter sensors coupled with optical imaging encompass all three future directions. Glutamatergic signaling is being interrogated through the use of engineered proteins that detect changes in extracellular glutamate concentrations.[6] This strategy for monitoring chemical transmission utilizes optical microscopy for signal detection, in lieu of directly implanted sensors. Advantages include single-cell resolution across large numbers of neurons. Efforts are underway to engineer genetically expressed sensors for a variety of neurotransmitters with the additional goal of enabling multiplexed detection. In many ways, this approach epitomizes our expanding ideas about the field of monitoring molecules in neuroscience.

In closing, I want to take this opportunity to thank the authors whose work is included in this special issue, as well as the many anonymous reviewers whose critical feedback greatly improved these contributions. Moreover, I want to express my sincere gratitude to the local organizers of the Monitoring

Molecules in Neuroscience 15th International Conference, and most notably Nigel Maidment and Kate Wassum. Without your creative insights and hard work, this meeting and issue of *ACS Chemical Neuroscience* would not have been possible. *ACS Chemical Neuroscience* editors and staff look forward to contributions to the journal from the monitoring molecules community in 2015 and beyond, and to being a central part of the realization of the future whose course has been charted here.

Happy New Year!

Anne M. Andrews, Associate Editor

■ AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

■ REFERENCES

(1) Wightman, R. M. (2015) Monitoring Molecules: Insights and Progress. *ACS Chem. Neurosci.*, DOI: 10.1021/cn500324m.

(2) Andrews, A. M. (2013) The BRAIN Initiative: Toward a Chemical Connectome. *ACS Chem. Neurosci. 4*, 645.

(3) Sarter, M., and Kim, Y. (2015) Interpreting Chemical neurotransmission in Vivo: Techniques, Time Scales, and Theories. *ACS Chem. Neurosci.*, DOI: 10.1021/cn500319m.

(4) Wassum, K. M., and Phillips, P. E. (2015) Probing the Neurochemical Correlates of Motivation and Decision Making. *ACS Chem. Neurosci.*, DOI: 10.1021/cn500322y.

(5) Cho, Y. K. (2015) Genetically Encoded Tools: Bridging the Gap between Neuronal Identity and Function. *ACS Chem. Neurosci.*, DOI: 10.1021/acschemneuro.5b00008.

(6) Liang, R., Broussard, G. J., and Tian, L. (2015) Imaging Chemical Neurotransmission with Genetically Encoded Fluorescent Sensors. *ACS Chem. Neurosci.*, DOI: 10.1021/cn500280k.