Molecular neuroscience: challenges ahead

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***Peter Seeburg** obtained his PhD in Genetics at the University of Tübingen in 1975. In 1987, he obtained a professorship at the Center for Molecular Biology at Heidelberg University in Germany and in 1996 became Director of the Department of Molecular Neurobiology at the Max Planck Institute for Medical Research. His lab elucidated the molecular and functional complexity of GABA-A receptors, the main inhibitory receptor channels in the central nervous system and, in collaboration with Bert Sakmann's lab, determined the molecular and functional subtypes of ionotropic glutamate receptors mediating fast excitatory synaptic neurotransmission. His current work generates gene-targeted mice expressing functionally altered glutamate-gated channels to study the role of glutamate receptor subtypes in hippocampal synaptic plasticity and spatial learning.*

A molecular neuroscientist with a pessimistic bent might feel that his field is coming to a close, seeing that most molecules contributing to a neuron's well-being and functional states are now known to us. There will still be unexplored ion channels and transcription factors in our genome, but isn't it merely a matter of time before these will be dragged onto the experimental stage? His colleague with an optimistic outlook, exulting in the great possibilities that molecular tools put at our disposal, will see himself more at the dawn of molecular neuroscience. The realist takes his position somewhere between these two extremes, realizing that he faces major challenges if he desires to contribute meaningfully to neuroscience by continuing to explore the molecular terrain. I will list a few examples, of which I hasten to say that they represent my personal preference rather than what may be the most pressing priority within the molecular neuroscience community at large.

The challenges begin with the grouping of proteins into functional complexes, as they operate in neural cells, preferably *in vivo*. We are well aware of the fact that most biological machines are assembled from sets of protein/transmembrane protein entities, but in only few instances are we able to reconstitute such a 'machine' from its parts with properties resembling those measured *in vivo*. A picture book example is the work on complexes of AMPA receptors and their auxiliary subunits, the TARPs, by the labs of R. Nicoll and D. Bredt, which demonstrated that the functional properties of AMPA receptors, as assessed by *in vitro* expression systems, required major modification to render them akin to those of postsynaptic AMPA channels. Such territory remains uncharted for most transmitter receptors and voltage-gated ion channels. Jumping across the synaptic cleft, we are painfully aware that we are unable to reconstitute the players and events at the presynaptic fusion pore to account for the submillisecond transmitter release following an action potential. In many cases failure to reconstitute molecular machines with correct properties might reflect a missing constituent. Hunting for the constituent is difficult and time consuming as anyone using genetic interaction screens can attest, whereas tagging the complex by genetic means, its isolation and analysis by modern mass spectroscopy provide promising alternative avenues. Naturally, the successful reconstitution of biological machines is prerequisite

to their structural elucidation, which will however take decades barring a quantum leap in determining the structure of membranous protein complexes.

The legion of cells that make up the brain can be classified according to numerous criteria. We commonly divide them in glial cells and neurons, and both of these major cell classes can be subdivided further. We expect a hippocampal CA1 pyramidal cell to differ from its presynaptic partner, a fast spiking parvalbumin-expressing GABAergic interneuron, in its gene expression and hence, the state of its chromatin, which ensures the appropriate transcriptional activity in this cell type. Knowledge of this 'chromatin code' for the many neural cell types, as well as of the dynamic range that the chromatin state can undergo in response to diverse activity, is highly desirable but difficult to attain. Valiant attempts are underway to mark different cell types with fluorescent proteins by use of cell-type selective promoters, isolate these cells by laser dissection microscopy and obtain gene expression profiles from RNA. But I suspect that a more systematic communal large-scale approach will be required before we can define cell populations in the brain by their chromatin code. One beneficial corollary should be the knowledge of the plasticity of this code in health and disease. Another is the genetic access to the different cells by knowledge of which select genes or combinations thereof are expressed in them. This, in combination with recombinant viral vectors, should greatly advance the precise placement by genetic means of the increasing number of powerful molecular tools, of which optogenetic photostimulation, developed by K. Deisseroth in collaboration with G. Nagel and E. Bamberg, provides an elegant example, by which we can inhibit or excite select neurons in the brain. We are furthermore in great need of temporal control of gene expression in select cell populations of the brain, permitting us to switch back and forth between expression states A and B for genes of interest, akin to the tet-on and -off systems introduced by M. Gossen and H. Bujard in 1992. This becomes a particularly pressing issue in the surging area of evaluating links to behavior and cognition.

In conclusion, molecular approaches will continue by ingenious innovations to make inroads in neuroscience at the interface of physiology, cell biology and genetics. By its versatile nature, molecular biology ensures its contribution to our understanding of the workings of the brain. This is the good news! The bad news is that we need to wait to find out how.

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