The modular multiprotein nature of these durable changes may be due to removal or turnover of master organizing molecules. Consistent with this notion, we have shown that the postsynaptic scaffolds Shank, GKAP, and AKAP79/150 undergo selective activity-dependent ubiquitination (*16*). Shank and GKAP are multivalent adaptors that bind to each other and to numerous additional proteins in the PSD (*5*, *20*). In addition, AKAP79/150 anchors PKA and PP2B to complexes containing AMPA receptors or NMDA receptors and PSD-95 family members (*21*). The ubiquitin-dependent removal of one or more of these scaffolds could provide a mechanism for selectively destabilizing numerous associated proteins in the PSD complex, thereby accounting for the clusters of proteins coregulated by activity.

The PSD is, in essence, a proteinaceous signal-processing machine, with scaffolds, receptors, and enzymes comprising the various gears (*3*). Our findings indicate that the molecular components of this machine accumulate or disperse in reproducible patterns influenced by activity level and ubiquitination, raising the possibility that the signaling properties of the PSD machine are similarly plastic. To address this question, we examined the effect of alterations in activity on downstream signaling to CREB and ERK-MAPK: two prominent signal transduction cascades organized by proteins in the PSD and involved in synaptic plasticity (*4*, *19*, *22*). Our results indicated that NMDA receptors at active synapses elicit augmented activation of CREB, whereas their counterparts at inactive synapses are selectively coupled to ERK-MAPK (*16*). This reciprocal regulation of CREB and ERK-MAPK pathways provides clear evidence that activity-dependent reorganization of the postsynaptic apparatus regulates multiple facets of synaptic signaling.

Thus, far from being an immutable structure, the PSD contains hidden dimensions of interconnected protein networks within which reside the molecular traces of experience. By demonstrating that activity controls the global composition of the synapse through ubiquitin-dependent turnover, our research provides a new conceptual framework for understanding and ultimately predicting functional changes in neural circuits.

References

1. R. Yuste, T. Bonhoeffer, *Annu. Rev. Neurosci.* **24**, 1071 (2001).
2. C. Luscher, R. A. Nicoll, R. C. Malenka, D. Muller, *Nature Neurosci.* **3**, 545 (2000).
3. M. B. Kennedy, *Science* **290**, 750 (2000).
4. H. Husi *et al.*, *Nature Neurosci.* **3**, 661 (2000).
5. M. Sheng, M. J. Kim, *Science* **298**, 776 (2000).
6. V. N. Murthy, T. Schikorski, C. F. Stevens, Y. Zhu, *Neuron* **32**, 673 (2001).
7. Y. Geinisman, L. deToledo-Morrell, F. Morrell, *Brain Res.* **566**, 77 (1991).
8. N. Toni *et al.*, *Nature* **402**, 421 (1999).
9. T. Meyer, K. Shen, *Trends Cell Biol.* **10**, 238 (2000).
10. G. G. Turrigiano, S. B. Nelson, *Curr. Opin. Neurobiol.* **10**, 358 (2000).
11. A. Rao, A. M. Craig, *Neuron* **19**, 801 (1997).
12. R. J. O'Brien *et al.*, *Neuron* **21**, 1067 (1998).
13. R. Malinow, R. C. Malenka, *Annu. Rev. Neurosci.* **25**, 103 (2002).
14. T. C. Thiagarajan, E. S. Piedras-Renteria, R. W. Tsien, *Neuron* **36,** 1103 (2002).
15. K. O. Cho, C. A. Hunt, M. B. Kennedy, *Neuron* **9**, 929 (1992).
16. M. D. Ehlers, *Nature Neurosci.* **10,** 10 (2003).
17. A. E. West *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **98**, 11024 (2001).
18. O. Steward, E. M. Schuman, *Annu. Rev. Neurosci.* **24**, 299 (2001).
19. J. P. Adams, J. D. Sweatt, *Annu. Rev. Pharmacol. Toxicol.* **42**, 135 (2002).
20. T. Boeckers *et al.*, *J. Neurochem.* **81**, 903 (2002).
21. J. J. Michel, J. D. Scott, *Annu. Rev. Pharmacol. Toxicol.* **42**, 235 (2002).
22. B. E. Lonze, D. D. Ginty, *Neuron* **35,** 605 (2002).

2003 Grand Prize Winner

Michael Ehlers grew up in Grand Island, Nebraska, and earned his bachelor's degree in chemistry from Caltech in 1991. He went on to the Johns Hopkins University School of Medicine, where he was awarded M.D. and Ph.D. degrees in 1998 and where he also conducted postdoctoral research. Dr. Ehlers is currently assistant professor of Neurobiology and director of the Neuroproteomics Laboratory at Duke University. His research focuses on the interface between neuronal cell biology and the plasticity of neural circuits, with emphasis on protein trafficking and turnover mechanisms in dendrites. He has won several other awards in neuroscience and is a Scholar of the Ruth K. Broad Foundation.

Karel Svoboda, for his essay "Imaging Experience-Dependent Synaptic Plasticity in the Adult Neocortex in Vivo." Dr. Svoboda grew up in the Czech Republic and Germany and received his bachelor's degree in physics from Cornell University in 1994. As a graduate student in biophysics at Harvard University, he measured the tiny steps and forces produced by individual kinesin molecules. After being awarded his Ph.D. in 1994, he pursued postdoctoral work at Bell Laboratories, where his interests shifted to synaptic and dendritic function and plasticity. Dr. Svoboda started his own laboratory at Cold Spring Harbor Laboratory in 1997. Work in his laboratory focuses on experience- and activity-dependent plasticity in the cortex, probed with imaging, physiological, and molecular tools.

Satchin Panda, for his essay "Shedding Light on Non–Image-Forming Photoperception in Mammals." Dr. Panda was born and raised in India, where he earned his bachelor's degree in plant biology from Orissa University of Agriculture and Technology. He joined the graduate program at the Scripps Research Institute, where he studied the circadian oscillator mechanism in plants in the laboratory of Dr. Steve Kay. Since receiving his Ph.D. in 2001, he has pursued postdoctoral research in Dr. John Hogenesch's lab at the Genomics Institute of Novartis Research Foundation, San Diego. Here he uses genetic and genomic approaches to gain an understanding of the light input pathway and of circadian regulation of behavior and physiology in mammals.

Rudolf Cardinal, for his essay "Succumbing to Instant Gratification Without the Nucleus Accumbens." Dr. Cardinal was born in Norwich, UK, and grew up in Folkestone, UK. He studied medical sciences and neuroscience at the University of Cambridge, where he received his bachelor's degree in 1996 and then pursued intercalated courses in clinical medicine and surgery with a Ph.D. in behavioral neuroscience, supervised by Prof. Barry Everitt. He was awarded his MB BChir Ph.D. in 2001. His Ph.D. thesis examined the neuropsychology of reinforcement processes, including the contribution of the anterior cingulate cortex to Pavlovian conditioning and the neuroanatomy of impulsive choice. After qualifying, he worked as a house physician and surgeon in East Anglian hospitals and is now a neuroscience lecturer at Cambridge.

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