Molecular Biology of the Brain, edited by S.J. Higgins. Princeton, NJ: Princeton University Press, 1999. 196 pp. $32.50.

The brain is one of the most complicated of all evolutionary adaptations, and is probably the most intriguing. How the complexities of human thought, language, cognition, consciousness, and emotion emerge from the myriad of deterministic interactions between various molecules at the most basic level is one of the greatest and most important questions facing science. The *Molecular Biology of the Brain* reviews the state of current knowledge about the molecular foundations of brain function and gives the reader an excellent window into some of the recent research aimed at trying to unravel the mechanisms by which the brain works (or fails to work). Written by leading researchers in this field, the volume is divided into 14 chapters that focus on a variety of questions surrounding neuronal growth and degeneration, synaptic transmission, cellular metabolism, and the molecular bases of various brain disorders and diseases. Each chapter has its own introduction, an excellent summary of the key points discussed, and a list of references specific to that particular chapter. The writing is, for the most part, clear and concise, though it is definitely not a book for a general lay audience. This book would be appropriate for a high-level undergraduate course in molecular biology, as well as for graduate courses. It would also be appropriate for individuals with a background in molecular biology who are interested in reviewing the latest research relevant to the brain. The level of prior knowledge assumed does vary from chapter to chapter, leaving some chapters much more accessible to a broader audience than others. This is the inevitable result of having different sets of authors for different chapters. The payoff is that this reasonably small book is crammed with information. Several chapters illustrate nicely how recent molecular biological techniques (such as the use of recombinant expression systems, 'knock-out' genes, and so forth) are being used to probe the mysteries of brain structure and function.

Chapter 1, written by Guy Tear, is titled "Molecular Cues that Guide the Development of Neural Connectivity." Tear reviews the molecular cues, both diffusible and substrate-bound, that guide axonal growth. A number of such signaling molecules are known, which act either as attractants or repellants: netrins, semaphirins, neuropilins, Eph receptor tyrosine kinases, ephrins, and CAMs ("cell adhesion molecules"). Many of these behave as axonal attractants in one molecular context and repellants in another. Tear discusses how these signaling molecules appear to affect the growth of the axon by reorganizing the neuronal cytoskeleton. In this chapter, one gets an excellent sense of the extremely complicated and intricate nature of the cellular interactions involved in growth and development of the nervous system.

Chapter 2, by Mark Wheatley, reviews the current knowledge of neurotransmitter receptors, which can be divided into G-protein-coupled receptors (which affect membrane potentials via effectors) and ligand-gated ion channels. These two classes differ in molecular architecture. Interestingly, there are usually

more than one receptor for a given neurotransmitter, with different receptor types typically showing different responses to various agonists and antagonists. Wheatley nicely summarizes research aimed at delimiting functional areas of the receptors.

In chapter 3, Giampietro Schiavo and Gudrun Stenbeck outline the details of neurotransmitter release, focusing on the last steps leading up to exocytosis of the neurotransmitter-containing small synaptic vesicles. The various proteins known to be involved in the cascade of interactions that control this process are discussed, including the "SNARE" proteins, synaptotagmin, Rab3A and Rab3C, and phosphoinositide. Also included is a short discussion of the probable role of the cytoskeleton in synaptic vesicle mobilization, as well as hypotheses regarding the proteins involved in synaptic vesicle endocytosis.

Chapter 4 covers the role mitochondria play in neuronal life and death. Samantha L. Budd and David G. Nicholls review the substantial evidence that disturbances in mitochondrial oxidative phosphorylation (either due to mutations in mitochondrial DNA [mtDNA] itself, or due to mitochondrial inhibitors) play a key role in a number of important brain diseases, such as Parkinson's, Alzheimer's, and Huntington's. This chapter will be of interest to anthropological geneticists because of the role mtDNA has played in hypotheses about the evolution of *Homo sapiens*. The models of genetic evolution used to evaluate the coalescence date for modern human mtDNA assume that selection has not been operating. The fact that major debilitating brain diseases are associated with mtDNA mutations, along with the obvious fact that the brain has been increasingly important during human evolution, suggest that the assumption of neutral change is not a good one, and therefore that coalescence dates of ~200,000 years ago suggested in the literature are not reliable (see Relethford 1998 for a recent review of this work). While Budd and Nicholls do not address these anthropological questions at all, this demonstrates the relevance this book has across disciplines.

Pico Caroni reviews the evidence for neuroregeneration and plasticity in chapter 5. The specific molecular factors, both intrinsic (within the damaged neuron itself) and extrinsic, that are known to be involved in the process of regeneration are discussed. The search for possible molecular strategies to maximize regeneration after damage is also covered.

Chapter 6, by Dominique Massotte and Brigitte L. Kieffer, covers opiates and the opiate receptor system. Opiates are some of the strongest analgesics and are also highly addictive (e.g., morphine). The authors discuss what is currently known about the complexity of the receptor system and discuss attempts to take advantage of this complexity to find less addictive opiates.

In chapter 7, Jane E. Haley covers the signaling actions of two simple gases: nitric oxide (NO) and carbon monoxide (CO). These molecules are not neurotransmitters in the traditional sense, but do seem to have clear signaling functions. NO appears to play a key role in the development of long-term potentiation (LTP) in the hippocampus, and thus is believed to play a crucial role in learning and

memory. The possible molecular mechanisms by which NO might serve as a retrograde messenger (which is crucial to induction of LTP) is reviewed.

Chapter 8 covers the molecular biology of the olfactory receptors. Yitzhak Pilpel, Alona Sosinsky, and Doron Lancet review the complexities of the olfactory receptor gene superfamily (which apparently accounts for ~1% of the entire typical mammalian genome). The biochemical cascade involving the transduction of odorant into neuronal action potential is covered, along with a discussion of how olfactory receptor genes are distributed in olfactory neurons (only one olfactory receptor gene appears to be active in any given olfactory neuron), and how these neurons are organized in the olfactory bulb itself.

Philip G. Strange covers the molecular biology of schizophrenia in chapter 9. Much of the work in this area has focused on the dopamine system. This chapter covers research on the possible elevation of dopamine function in the brain (either through increased levels of the neurotransmitter itself or through increase numbers of dopamine receptors). Evidence for increases in the number of receptors is equivocal; evidence for increased dopamine release is stronger. Changes in brain structure (i.e. increased lateral ventricular size, reduced temporal lobe size, functional differences in prefrontal function) are mentioned. Research on antipsychotic drugs and their probable effects on dopamine receptors in the brain are also covered.

Chapter 10, by Michael Hutton, Jordi Perez-Tur, and John Hardy, covers the genetics of Alzheimer's disease (AD). The majority of the chapter covers the early-onset (autosomal dominant) form of the disease, which appears to be caused by mutations in either one of the presenilins or in the amyloid precursor protein itself (amyloid deposits in the brain are a defining characteristic of Alzheimer's). However, early-onset AD represents less than 10% of all cases. Less discussion is devoted to the much more common late-onset form of Alzheimer's, which appears to be caused by a mutation in apolipoprotein E (involved in mediating cholesterol distribution between organs).

Chapter 11 covers current research on prion diseases, focusing specifically on Creutzfeldt-Jakob disease. Written by Adriano Aguzzi, Michael A. Klein, Christine Musahl, Alex J. Raeber, Thomas Blattler, Ivan Hegyi, Rico Frigg, and Sebastian Brandner, this chapter is probably the least accessible to a broad audience. The authors discuss the use of neural grafts into prion-protein-deficient mice to investigate the spread and toxicity of prions in the brain. This work suggests that the disease-causing isoform of the normal prion protein is not inherently toxic itself. Instead, pathology seems to be caused either by the inability of the cells to deal with endogenously produced abnormal prion protein, or by the initiation of conversion of normal to abnormal prion protein in cells that already produce normal prion proteins. Their neural graft techniques also show that the spread of the disease in the brain depends on expression of normal prions in adjacent cells.

In chapter 12, Astrid Lunkes, Yvon Trottier, and Jean-Louis Mandel discuss

a number of brain diseases that appear to be caused by unstable expansions of trinucleotide or dodecamer repeats in the genes for different proteins. The best known of these (and the one the authors spend the most time discussing) is Huntington's disease (HD), which results in the progressive degeneration of motor function, cognitive impairments, and mood disturbances (leading inexorably to death), all of which appear to be the ultimate result of polyglutamine expansions in the protein huntingtin. The authors discuss research showing abnormal intracellular aggregations of this mutated protein in HD patients. At least 14 other brain diseases are known to be caused by such expansion of repeats (the key specifics of which are outlined in a table in this chapter.)

Chapter 13 is an excellent review of the fascinating research into the molecular biology of memory and learning. Emily P. Huang and Charles F. Stevens discuss the dominant hypotheses about how learning and memory are mediated at the neuronal level, the studies supporting the importance of long-term potentiation (LTP) in this process, the role of the NMDA receptor activation in LTP, and the cascade of molecular interactions which underlie LTP. Research consistent with the idea that long-term memory formation requires structural changes in neurons (involving protein synthesis) is also reviewed, along with studies implicating the importance of cAMP (via cAMP-response-element-binding protein) in this process.

Finally, chapter 14, written by Susan Greenfield, reviews the diversity of signaling mechanisms that occur in the brain, many of which do not fit the classical model of a neurotransmitter (e.g., NO, as discussed in chapter 7). The need to think in more global, holistic, and integrative terms about neuronal communication is emphasized.

In summary, this book does exactly what it sets out to do, and I recommend it to anyone with an interest in the molecular details of how the brain works (though having some background in molecular biology makes it an easier read). It is also useful in that, being an edited volume, individual chapters stand on their own. One can, therefore, focus easily on topics of one's own particular interest (and include only a few pertinent chapters in a course reader, for example).

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Literature Cited

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