Chapter highlights: Potential Therapies (Ch 15)

The purpose of “chapter highlights” is to offer a framework in which to think about the specific information discussed in each Brain Facts chapter. These highlights draw upon information in the chapter and on the new Brain Facts web site (http://www.brainfacts.org) and occasionally, on our own knowledge of neuroscience that may not be discussed in Brain Facts. Questions for Brain Bee will come from Brain Facts (new 2012 publication) and entries from the new Brain Facts web site that have “brainfacts.org” in the URL. Some but not all relevant entries are cited below. Questions to guide your studies are noted in italics.

You may be surprised to learn that many drugs used today were developed by trial-and-error techniques or were discovered by accident.

You may also be surprised to learn that it works both ways: while neuroscience research lays the ground work for development of new drugs, drugs can also provide insight into basic mechanisms of brain function and/or dysfunction.

Example: A classic example is a drug, Reserpine, which was given to patients to lower high blood pressure. It was soon discovered that such patients also tended to become depressed. Because this drug works by lowering monoamine activity, this gave rise to the idea that the monoamine system was involved in the control of mood and that reduced monoamine activity in the brain may cause depression. Some medicines used today treat depression by increasing activity of the monoamines. (Can you list which neurotransmitters the monoamines include?) Reserpine itself was later used to treat psychotic symptoms (e.g., undue agitation that can occur in patients suffering from schizophrenia) but has been replaced more recently by newer drugs that have more select action in the brain with fewer side effects.

To emphasize--A major goal behind developing new drugs is to have more select action in the brain with fewer side effects.

Working to identify and understand basic mechanisms in biology, even in plants, can offer new potential therapies for treating brain disorders and disease in humans.

Example: Recent discovery of a light-sensitive channel (called Channelrhodopsin-2) in algae may lead to new therapies that offer unrivaled specificity. To learn more, go to http://www.brainfacts.org/about-neuroscience/technologies/articles/2008/light-molecules/. Optogenetics (uses light and genetic engineering) offers the possibility of treating only the affected or diseased neurons while not disturbing the normal function of healthy neurons.

Can you envision how optogenetics might be used to improve the therapeutic efficacy of deep brain stimulation for treating Parkinson’s disease (PD), a late-onset neurodegenerative disease?

Do you know? Neurons affected by PD use what neurotransmitter and die in what part of the brain?

Go to: http://www.brainfacts.org/diseases-disorders/degenerative-disorders/ to learn more about PD.
Go to: http://www.brainfacts.org/about-neuroscience/animals-in-research/animal-research-success-stories/articles/2012/animals-psychiatric-disorders/ to see how optogenetics has the potential to enhance our understanding of which neural circuits are involved in psychiatric disorders.

**Methods in molecular biology are being used to develop or discover new drugs and/or improve old ones.** Conducting basic scientific research leads to a better understanding of the role of individual genes and proteins in normal processes in the brain. This new information about basic cellular processes invariably leads to new ideas about therapeutic strategies for treating brain disorders.

**Many drugs of abuse and drug therapies target the synapse, the site of chemical communication between neurons and their targets.** To learn more about chemical transmission and its role in brain disease, go to http://www.brainfacts.org/brain-basics/cell-communication/articles/2011/neurotransmitters-how-brain-cells-use-chemicals-to-communicate/ Specific examples of drugs of abuse that alter normal chemical transmission between neurons include cocaine, marijuana, heroine, amphetamine, and morphine. Do you know which chemical system each drug interacts with?

Specific examples of drug therapies that target the synapse in brain disorders or disease include L-dopa to treat PD, SSRIs to treat depression, valium to treat anxiety and rivastigmine to treat Alzheimer’s disease (AD).

**Drug therapies often exploit or mimic biological mechanisms that exist in nature.** Examples include:

- **antibodies or interfering RNAs** (the body and cells natural defenses against foreign or potentially threatening molecules) may someday be used to effectively neutralize (antibodies) or prevent the translation (RNAi) of mutant proteins that cause neurodegenerative disease.

  While autoimmune diseases such myasthenia gravis and multiple sclerosis can cause neuronal dysfunction (can you describe what antibodies attack in each case?) and lead to significant impairments in behavioral function, antibodies can also be used as a therapeutic strategy for promoting recovery of function.

  Example: antibodies directed against Nogo-A to promote nerve regeneration after spinal cord injury

  http://www.brainfacts.org/about-neuroscience/technologies/articles/2012/engineered-antibodies/

- **Cell and gene therapy:** the use of stem cells to replace dying cells and viral vectors (such as adeno-associated virus and lentivirus) to deliver normal functioning genes to compensate for faulty ones.

  While neuronal death is a hallmark feature of all neurodegenerative diseases, recent research on animal models indicates that the most effective therapies will likely be
those that correct cell function, not necessarily prevent cell death. Why? Once cell death genes are activated, it may already be too late to reverse the process and once the neurons have died, there are no neurons to rescue. But recent research makes it clear that neurons affected by disease show altered function well before cell death genes are activated. New drug therapies will attempt to correct cell function so that cell death pathways are never engaged.

**Animal models and gene engineering hold promise for genuine cures.** Thanks to relatively new methods in molecular biology, scientists now know the affected gene and the nature of the mutation for many inherited neurodegenerative diseases (*can you name some of these diseases?*) Once the gene is identified, the mutant gene can be expressed in cell and animal models. There has been an exponential growth in development of new animal models for studying neurodegenerative disease since 2000. Two significant advantages of these models are 1) it gives scientists the opportunity to study early stages of disease (this is important because it is probably when the effects of disease are most likely reversible) and 2) offers new avenues for identifying and understanding the basic molecular processes that underlie disease and thus, offers hope that genuine cures for neurodegenerative disease will be found.

Go to: [http://www.brainfacts.org/diseases-disorders/degenerative-disorders/](http://www.brainfacts.org/diseases-disorders/degenerative-disorders/) to learn more about neurodegenerative disease

Another approach includes harnessing the normal activity of molecular chaperones that help to maintain the native structure of proteins, important for proteins to perform their normal functions.

If molecular chaperones fail to correct the misfolding of proteins (often the case when proteins contain mutations that cause inherited neurodegenerative diseases such as Huntington’s disease (HD) and familial Amyotrophic Lateral Sclerosis), then molecular chaperones promote the degradation of these potentially harmful proteins. However, over the life span, the amount of misfolded proteins appears to accumulate in the affected cells, impairing their function and causing disease. This may explain why many inherited neurodegenerative diseases emerge in mid-life even though the mutant protein was expressed from early on.

Animal research has already shown that transgenic mouse models engineered to overexpress molecular chaperones can rescue mice from disease caused by the mutant HD protein.

In the mid to late 20th century, scientists discovered many trophic factors that normally play a role in keeping developing neurons alive during programmed cell death.

Nerve growth factor (NGF) is one such example mentioned in this chapter that has the potential to keep neurons alive that die during AD.