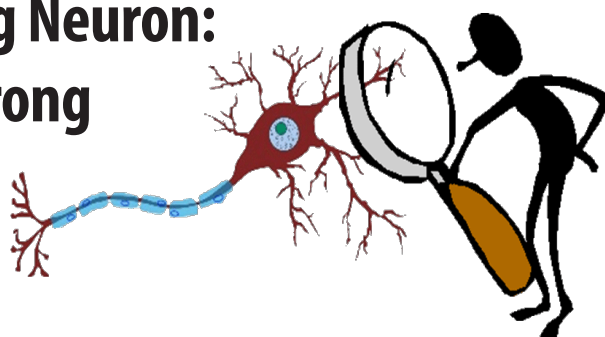


The Case of the Malfunctioning Neuron: When Cellular Processes Go Wrong

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Part I – The Nervous System

Joyce was sitting in her freshman biology class trying to connect the moving parts of protein synthesis. She couldn't concentrate however, and was particularly distracted. She had just been home for a long weekend to visit her parents and had noticed some peculiar things going on with her mom. When she and her mom were out shopping, her mom had been walking a bit funny. Her foot kept slapping against the ground. Joyce also had noticed that her mom was talking with a slight slur, something she had never heard before. At first, Joyce found it amusing. But this continued throughout the day and during her entire visit home. Joyce also noticed some twitching in her mother's forearms. Being a "pre-health" biology major, she started to wonder what was going on.

Joyce went up to her dorm room, opened up her textbook, and turned to the chapter on the brain. She read about how the brain is made up of billions of neurons, which are the basic cellular units of the brain. These neurons help people to think, respond to the environment around them, maintain homeostasis, and move.

"Aha!" Joyce said to herself. Maybe her mom's strange walking and speech had to do with how her neurons were working.

Joyce decided to ask her teacher after her next class how neurons communicated with each other and with muscles. Her teacher eventually directed her to a video and an article on how neurons function:

- Video 1: *2-Minute Neuroscience: The Neuron*, 2014: <<https://youtu.be/6qS83wD29PY>>
- *The Brain: Understanding Neurobiology—Neurons, Brain Chemistry and Neurotransmission*. National Institutes of Health, 2010. <<https://science.education.nih.gov/supplements/webversions/BrainAddiction/guide/lesson2-1.html>>

After examining neuron function, Joyce spent some time searching on the internet and came across a documentary video about a woman whose mom was diagnosed with a disease called Amyotrophic Lateral Sclerosis, or ALS:

- Video 2: *A Personal Story of ALS*, 2017: <https://youtu.be/_OL2YOTTp_k>

Joyce then did some research on what ALS is and watched a video about it:

- Video 3: *2-Minute Neuroscience: Amyotrophic Lateral Sclerosis (ALS)*, 2017. <<https://youtu.be/kOnk9Hh20eg>>

Questions

1. Draw a normal motor neuron and label the major parts of that neuron. Labels on the figure should include dendrites, cell body, axons, myelin sheath, and the neuromuscular junction. In comparison, draw what a neuron would look like in a person diagnosed with ALS.
2. As a biology student, it is important to understand that the human body is like a machine, made up of many individual parts that work together in a highly interactive and coordinated way. This coordination starts at the cellular level and goes all the way to the organismal level. Explain how cellular malfunction in the case of ALS can lead to the physical manifestations of patients with ALS. Second, explain why it is important to understand the cellular components of biology in order to understand health and human disease.

Part II – Linking Biology Lectures to Real Life

A month after her visit home, Joyce's dad called and revealed that her mom was in fact being tested for the possibility of having ALS. Testing for ALS is an arduous task since no real diagnostic test exists aside from ruling out every other possibility (MedicineNet.com, 2017). Joyce was shocked. "How could this be?" she thought to herself. Her mom was only 57 years old. Joyce has always assumed that diseases linked to the brain usually affected people much older than that. But she learned from her additional investigations that the average age of diagnosis for ALS was 55, although it can occur in people as early as their mid-twenties. It also was interesting to discover that her mom might have a disease that tends to affect men and people in the military more often. The most alarming statistic was that the disease was 100% fatal and that the life expectancy was only two to five years (ALS Association, n.d.). Joyce felt very disheartened and she was worried about her mom. She decided to try and figure out how this could happen. She discovered that most cases of ALS are sporadic, meaning that there is no real genetic link. However, approximately 10% of all cases of ALS are in fact inherited (ALS Association, n.d.).

Joyce began to think back to the lecture she was just in that morning. She was learning about the central dogma of biology and the flow of information from DNA to RNA to proteins and suddenly it began to come together for her in a "real world" scenario. She contemplated the idea of "misfolded proteins" and their possible role in ALS. She watched a video recapping what she had learned about protein formation:

- Video 4: *Protein Synthesis*, 2017. <<https://youtu.be/LqHnOn3Pk-w>>

Question

1. How is DNA involved in making proteins?
2. Briefly describe the overall process of protein production including where processes occur (transcription versus translation) and describe the roles of some of the major players including RNA polymerase, mRNA, tRNA, ribosomes, codons, amino acids, and peptide bonds.

Part III – When Things Go Wrong

Joyce now understood that DNA contains the information that codes for proteins. In addition, the segments of DNA that do code for particular proteins are called genes. Proteins are made by ribosomes based on the information given to them by the DNA, which is transcribed to mRNA for travel to the ribosomal site. The last step of protein synthesis is protein folding. The protein is folded precisely into a three-dimensional structure that is based on the order of the amino acids and can now play the correct biological role within the cell (Creighton, 1990). Mutations, which are changes to the DNA or the genetic sequence within a cell, can occur. Mutations can have no impact on protein production or they can have devastating consequences to the protein depending on which bases and the number of bases affected by the mutation (University of Utah, Genetic Science Learning Center, n.d.).

Joyce wondered if mutations could play a role in the development of ALS and did some searching for possible causes of ALS (Muscular Dystrophy Association, n.d.). She found that there are in fact a large number of genes that have been identified as possible contributors to the development and progression of the disease. She also remembered from the video she watched that described ALS that patients displayed protein aggregates or clumps of irregular proteins in and around the neurons.

One of the first mutations to be described in ALS patients was traced to mutations in the gene SOD-1 (Bunton-Stasyshyn, 2015). One of the functions of SOD-1 is to act as a sponge to a neurotransmitter called glutamate. Glutamate is a chemical released at the synaptic gap and is used to send a signal to the next neuron. So glutamate plays an important role in keeping the signals in the brain going. The bad part of glutamate is that it can be toxic if it accumulates to high levels at the synaptic gap. Research has shown that in addition to SOD-1 being mutated, ALS patients also display higher levels of glutamate in the fluid that bathes the brain and in the spinal cord when compared to controls (ALS Association: Disease Mechanisms, n.d.). If this excess glutamate builds up to high levels and the neurons get damaged, they may not be able to signal to the muscles, which can lead to the atrophy or destruction of the muscles that is seen in patients with ALS (Foran et al., 2009; Van Damme, et al., 2005).

Questions

1. Explain why it is so critical that protein production occurs properly in cells. Integrate how mutations affect this process into your answer.
2. Using words and a picture, describe how SOD-1 and glutamate are thought to be involved in the progression of ALS. Show a picture of a normal synapse with SOD-1 and glutamate and compare that to a neuron where SOD-1 is mutated and can't function properly.

Part IV – The Race to Find a Cure

A few months had passed before Joyce got the final word that her mother did in fact have ALS. The diagnosis devastated her entire family. They all knew that eventually this disease would take their mom, one muscle and one organ system at a time, but they were hopeful. They started to research what was being done to find a cure and see if there was anything they could do. The ALS Ice Bucket Challenge, begun in the summer of 2014, brought ALS to the forefront in the public fight to find cures for untreatable diseases. Millions of people participated by dumping a bucket of ice and water over their heads or another person's head (and capturing it on video) to promote awareness of ALS and encourage donations to research. The challenge became the world's largest global social media phenomenon. The start of this global phenomenon was credited to Pete Frates, a former Boston College baseball player who was diagnosed with ALS in 2012 at the age of 27. He and his friend Pat Quin, who also was diagnosed with ALS, are considered to be the founding fathers of this movement (Gallo, 2014). More than 17 million people uploaded their ice bucket challenge videos to Facebook and these videos were watched by about 440 million people a total of 10 billion times. Approximately \$115 million dollars were raised in 2014 alone as a result of this challenge. A large proportion of the money (67%) went to research. The rest of the money went to patient and community services (20%), public and professional education (9%) and the rest went to fundraising and processing (ALS Association: The ALS Ice Bucket Challenge, n.d.).

With all of this money being raised for research on ALS, Joyce couldn't help but question why a treatment or a cure hadn't been found yet. She began to question how "cures" were found. She learned that this process is much more complicated than she thought (Food and Drug Administration, 2017). She compiled her findings on the drug discovery process into the graphic shown below (Figure 1). She then went on to find out what was in the "pipeline," so to speak, for treating ALS patients. She found that there were two FDA approved drugs for ALS patients. One, Rilutek, was approved in 1995 and only gives patients on average a few more months of life (ALS Worldwide, 2015). The second drug is Radicava, which was approved in 2017. This drug offers hope for patients with ALS since clinical trial showed a 33% reduced decline in physical ability when compared to a control placebo group (Kegel, 2017). Joyce began to think about what happens if the new drug is not as successful as promised—what's next? Would we have to wait more than 20 years for another treatment possibility? Joyce realized how important it would be to get involved in the ALS community and to help in the fundraising and awareness efforts for this fatal disease in honor of her mom.

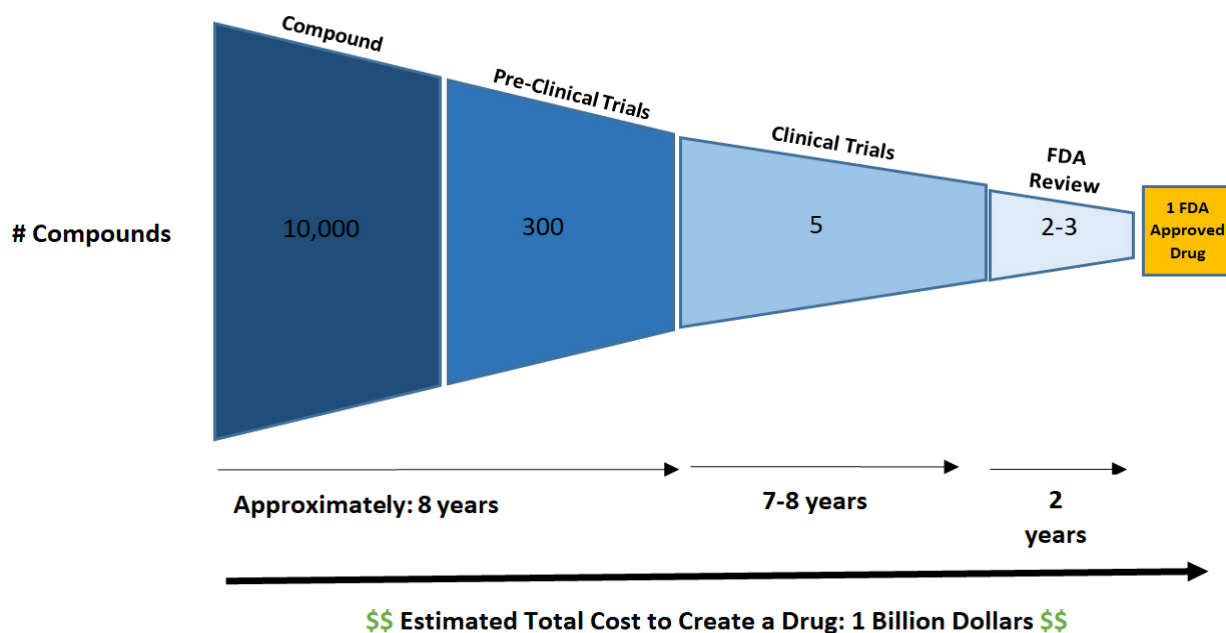


Figure 1: Drug Discovery Process. The total cost of the process compared to the success of compounds and the overall time it takes to get one compound to the market.

Question

1. A friend comes to you and argues against additional funding for research for a cure because she thinks that we already devote too much money to it. Can you come up with an argument for why so much money is needed and why additional funding is needed in most areas? Can you include the importance of the drug pipeline and what happens when that goes dry? Be sure to include the length of each phase of the studies and why it takes so long.

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