**POE #3: Botulinum Toxin**

**Topic**

Unit 3- Nervous Tissue (Neurotransmitter Dysfunction, Membrane Potentials, Synapses, Action Potentials)

The scenario below has been simplified for the purposes of this introductory anatomy and physiology course. As you progress in your academic and professional careers you may learn more extensive details related to this scenario.

**Introduction to the Phenomenon**

*As you read through the scenario below underline specific facts and information you find important to the situation*

Fred works on a farm every day of the week. To perform his daily farming tasks, he uses a number of tools and machines that require skillful handling. One day Fred was feeling fatigued, and as he was working with a pickax to dig up soil, he accidently swung the pickax and sliced his leg. Since Fred was working in deep soil, his open wound was exposed to bacteria living in the soil. Before being able to get back to his house, he had to trudge through another 50 feet of deep soil, which continued to expose his wound to bacteria. Unfortunately, his body was unable to defend against this prolonged exposure, and several days after Fred’s incident, the clostridium botulinum bacteria produced a dangerous toxin. When large amounts of this bacteria infiltrate the body, they begin to produce a toxin called botulinum toxin, which leads to numerous nerve and muscle complications. Fred didn’t realize he had been infected by this bacterium until he began experiencing numbness, tingling, and pain throughout his body and especially in his face. He also began to experience weakness in his muscles, and mild muscle paralysis. Upon experiencing these symptoms, Fred immediately called for medical assistance, and after hospitalizing Fred, the medical staff began to administer antitoxin in an attempt to rid his body of the botulinum toxin. Luckily Fred’s botulism was treated early enough to prevent further nerve and muscle damage, but if he had not been hospitalized, he would have experienced worse symptoms and potentially flaccid paralysis of his respiratory muscles.

**Driving Question(s)**

Why did the botulinum toxin cause nerve complications and mild flaccid muscle paralysis in Fred? If Fred did not receive medical attention immediately, would he have survived?

**Initial Hypotheses/Predictions**

*In the box below, please provide your initial ideas about a possible answer to the driving question(s) above.*

Answers will vary from student to student

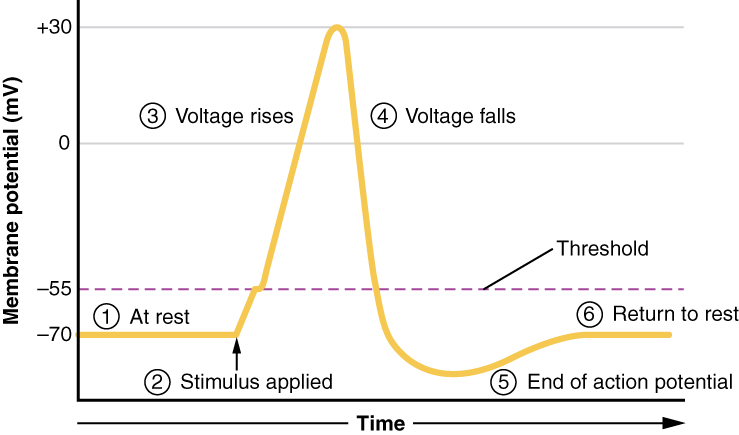
Predictions and hypotheses should be scientifically based

Possible answers to the driving questions should be described in this box

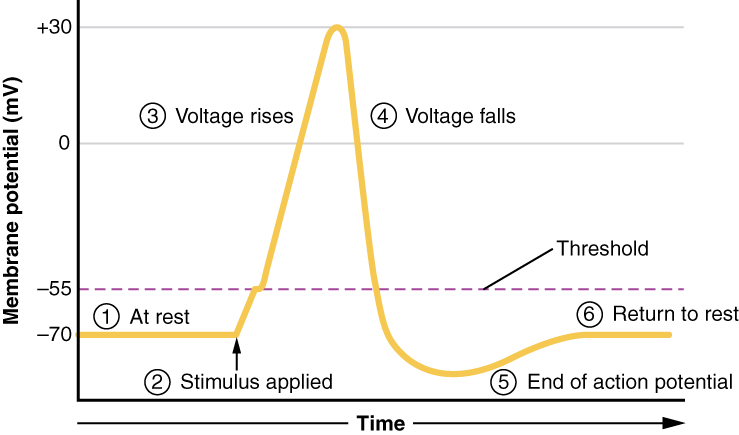
**Relevant Data & Analysis Questions**

***ALL analysis questions are italicized in the pages below***

**Normal Action Potential Graphs**



Action Potential Sent Down Presynaptic Neuron

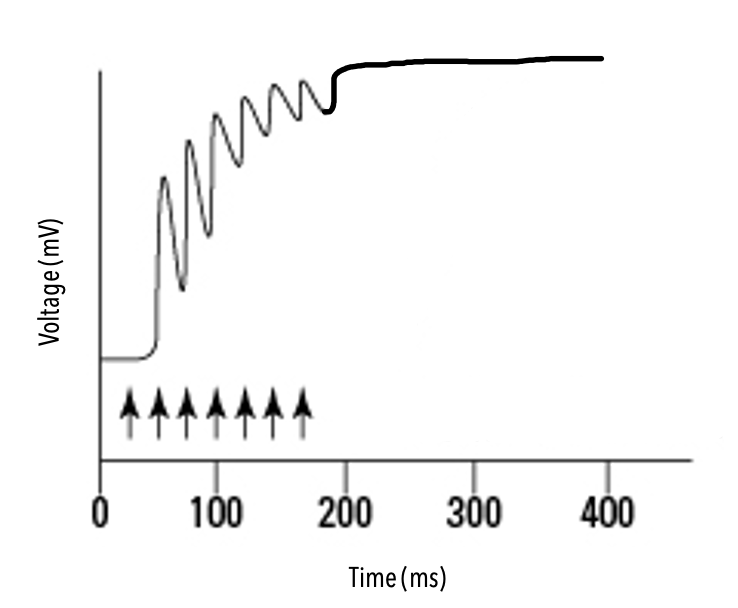


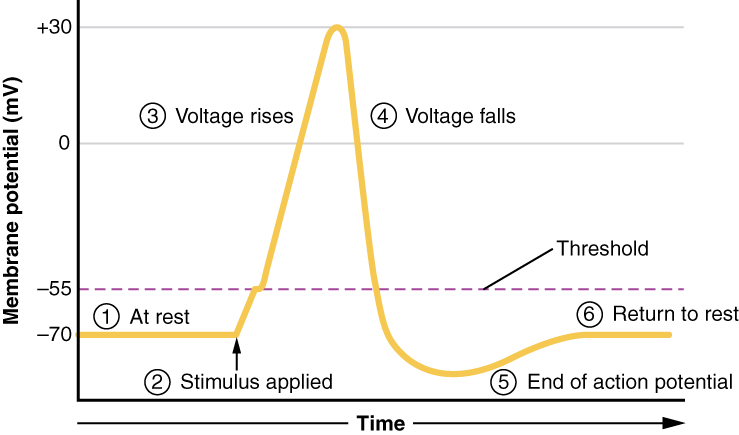
Normal Action Potential Initiated in Postsynaptic Nerves and Muscle Fibers

Acetylcholine

Released

**Sandy’s (our friend from POE Unit #2 is making a guest appearance) Action Potential Graphs**

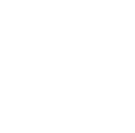
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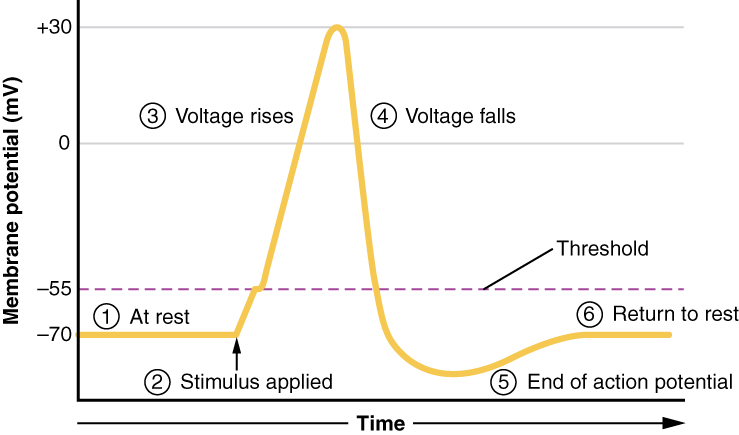
Action Potential Sent Down Presynaptic Neuron

Continual action potentials occurring in the postsynaptic nerve or muscle causing dysfunction and spasms due to constant sodium influx (Low Ca2+= Na+ channels open)

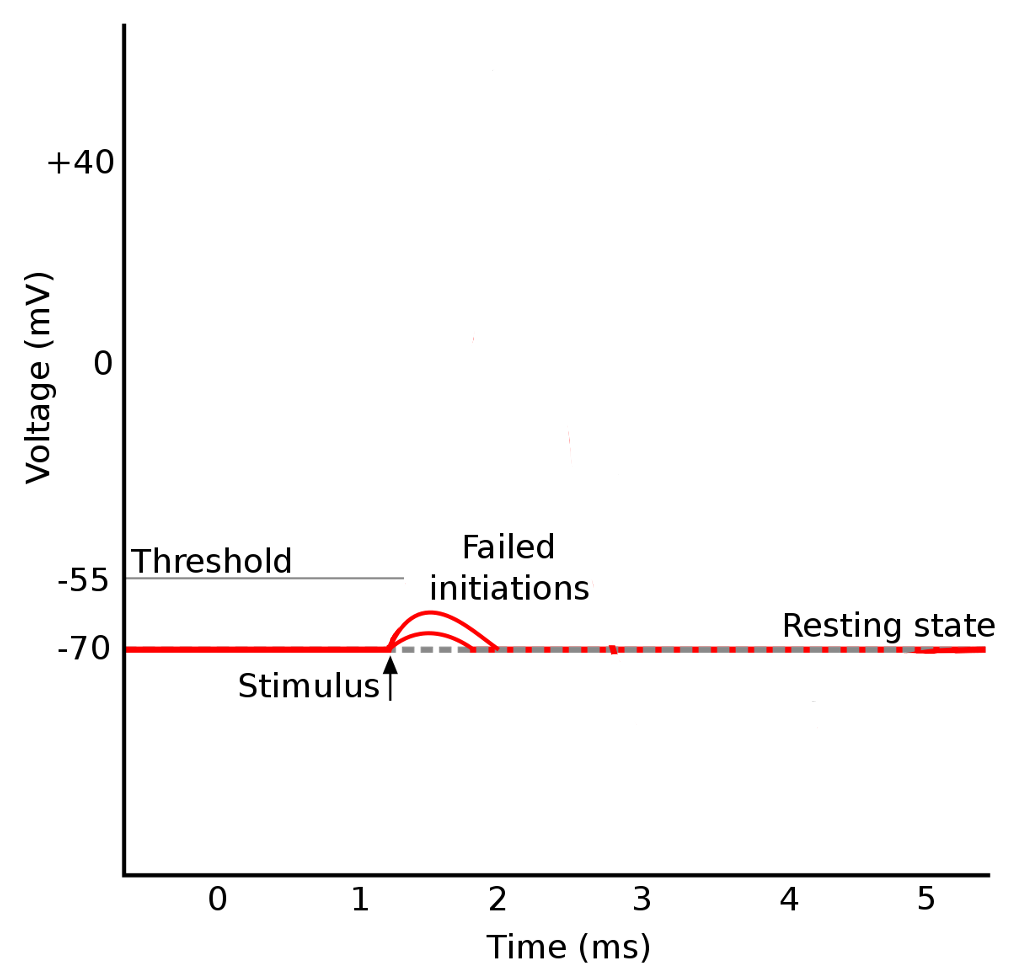
Acetylcholine Not Released (Due to lack of calcium)



**Fred’s Action Potential Graphs**



Action Potential Sent Down Presynaptic Neuron



*Why is there no action potential occurring in the graph above?*

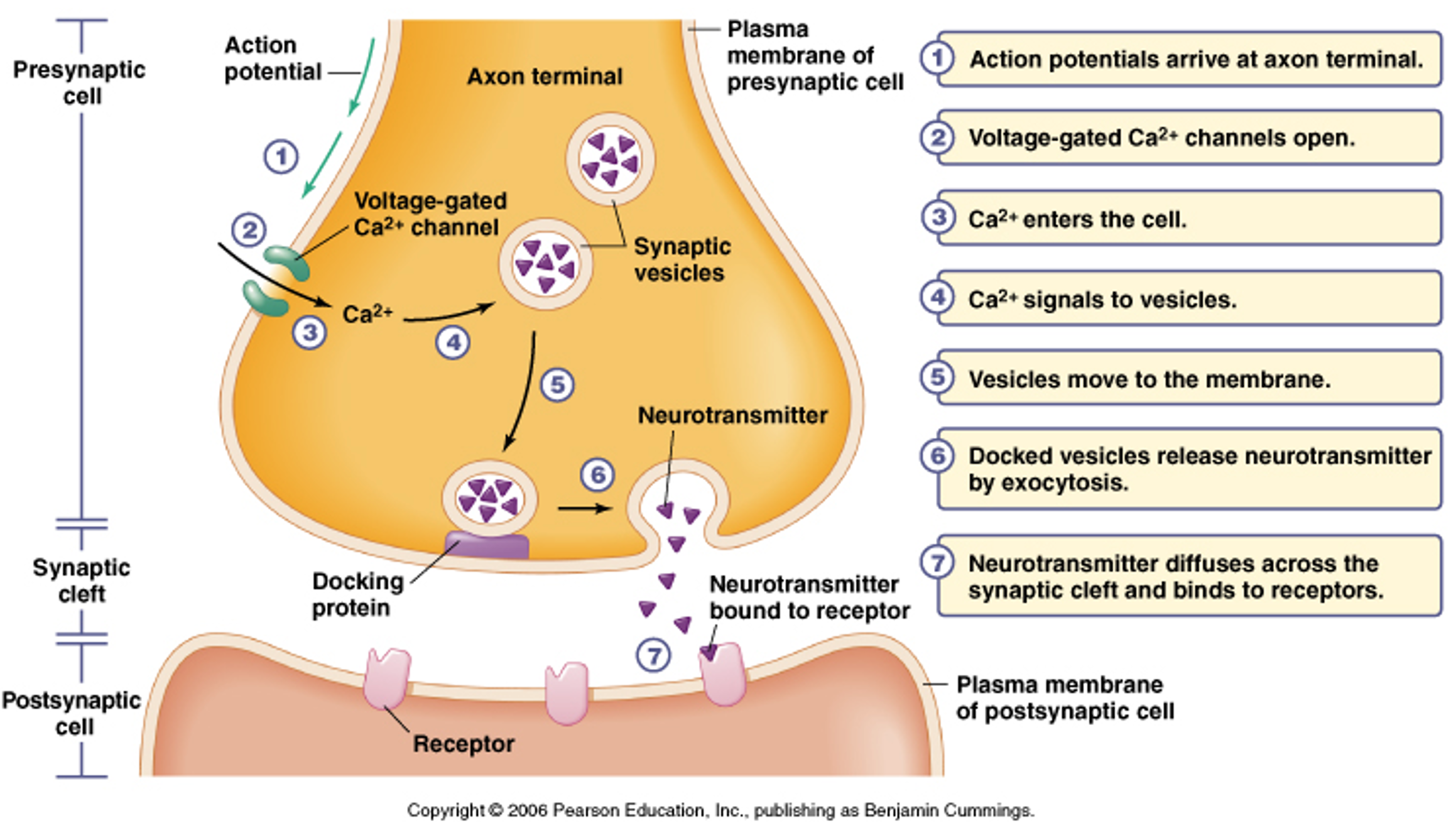
*There is no action potential, because acetylcholine is not being released, and without this NT, ion channels cannot open to change membrane potential and generate an action potential.*

Acetylcholine Not Released



*Remember from the unit 2 POE when Sandy experienced nerve dysfunction and muscle cramping/spasming due to low levels of Ca2+ in her body? Her issue was more related to calcium’s role in regulating sodium channels and neurotransmitters, because low calcium led to an increase in sodium entering the cell and a decrease in NTs being released. How is Fred’s situation different? What is happening to his action potentials and nerve/muscle communication? (Use the graphs above to help answer the questions)*

*Based on the action potential graphs we can see drastic differences in the action potentials occurring in Sandy’s case compared to Fred’s case. In Sandy’s case her neurons were sending signals to the receiving nerves and muscles but the lack of calcium led to a lack of NTs being released, which ultimately caused dysfunction in this communication pathway. The nerves couldn’t properly signal other nerves and muscles to function and contract properly and voluntarily. So, what happened was the lack of calcium caused sodium channels on the muscles to remain open and allowed sodium to freely flow through the membrane causing unwanted and random action potentials in the muscles. This led to constant and involuntary muscles contractions and spasms, and within the receiving nerve would lead to random nerve pains and signals. In Fred’s case the action potential is sent down the presynaptic neuron, and neurotransmitters are also not released, so the receiving nerve or muscle is not receiving the NT signals and cannot contract or function properly. But in his case, he has enough calcium, so something else is affecting the release of acetylcholine (the neurotransmitter). In Fred’s scenario it seems that the botulinum toxin is preventing the NTs from being released and signaling the post synaptic target cells, which is ultimately leading to failed action potentials and likely flaccid muscle paralysis.*

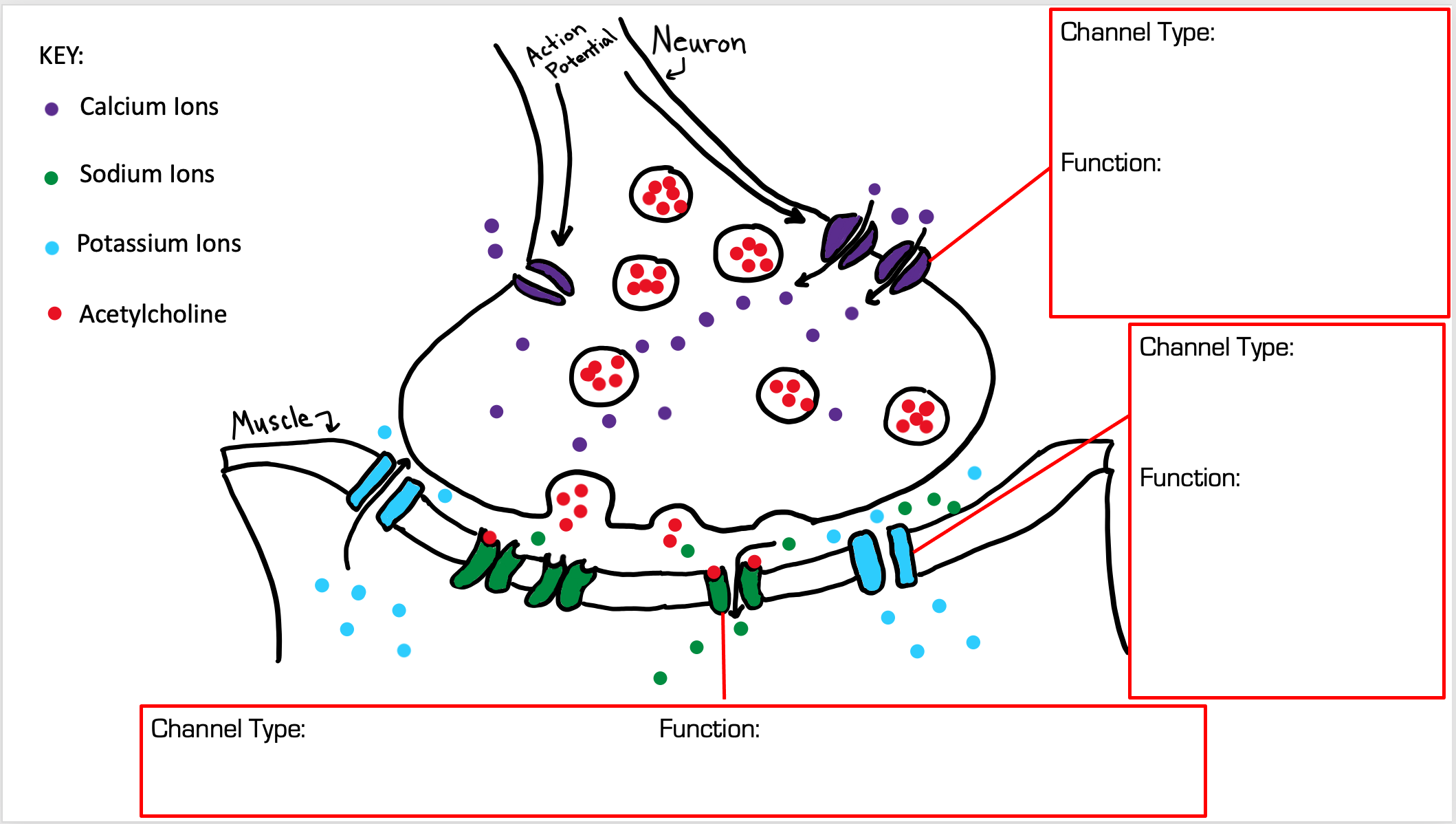
****Normal Neuromuscular Junction**

*Which* ***one*** *of the 7 steps above would be affected by botulinum toxin? Why? (Hint: Botulinum toxin can be found in the presynaptic neuron)*

*Step 6, because the botulinum toxin is found in the presynaptic neuron, and it cleaves proteins that allow the vesicles with neurotransmitters to dock and release acetylcholine. When acetylcholine is not released, there won’t be any binding of neurotransmitters on the ligand-gated ion channels. The lack of binding will keep the channels closed and prevent ion movement leading to a failed action potential in the muscle fibers and no muscle contraction.*

*In the graphic below, label the channel type and how that channel functions in the red boxes. Describe how the channels allow different ions to move within the neuromuscular junction:*

*(****HINT: Channel type options: Ion Leak Channel, Voltage-Gated Ion Channel, Ligand-Gated Ion Channel****)*



Ligand-Gated Ion Channel

Require a chemical messenger such as a NT to open the gate and allow ions to flow in and out

Ion Leak Channel

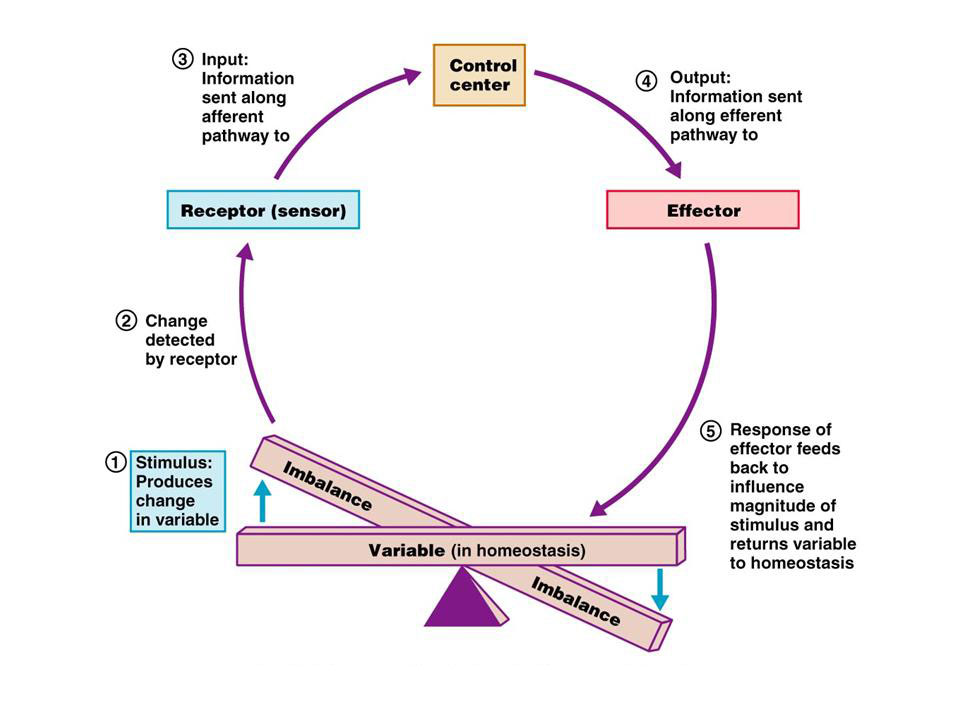
Voltage-Gated Ion Channel

Require a change in voltage (i.e. an action potential) to open and allow ions to pass in and out

These channels are constantly open and allow ions to flow freely down their concentration gradient

***Circle*** *where botulinum toxin would affect the neuromuscular junction in the image above.*

*Students should circle the neurotransmitter vesicles in the presynaptic neuron as these would be affected by botulinum toxin because the toxin prevents the release of acetylcholine.*

**General Homeostasis Pathway**

**Homeostasis Examples**

*Complete the table (Fill in the blanks)*

|  |  |  |
| --- | --- | --- |
| **Stimulus** | **Sensor/Control Center** | **Effector/Response** |
| Low Blood Glucose | Pancreas (Alpha Cells) | The alpha cells will release glucagon, which signals the liver to release its stored glucose (glycogen) into the blood to raise blood glucose levels |
| Low blood calcium | Parathyroid Gland (PTH) | Osteoclasts break down bone to release calcium into the blood |
| Decrease in body temperature | CNS (brain & spinal cord)  Peripheral nerves | Vasoconstriction of blood vessels  Increased muscle contractions (Shivering)  No secretion from sweat glands |
| Touching a hot surface | Nociceptors (in hand/skin)  Sensory Neurons  Brain/Spinal Cord | Signals sent down motor neurons to signal muscles to remove hand from the hot surface |

*In the unit 1 & 2 POEs we discussed examples of hormonal homeostasis. In this POE what type of homeostatic regulation is occurring? (i.e. is it hormonally driven or CNS driven?) Explain.*

*Due to the involvement of the nerves and muscles within neuromuscular junctions this POE, and Fred’s scenario is more of an example of CNS driven homeostasis. In Fred’s case his body is being infiltrated by an external toxin that prevents his nerves from properly communicating with other nerves and muscles. This disruption in normal nerve to nerve or nerve to muscle communication is a disruption of nervous system driven homeostasis. If the body is incapable of sending signals from neurons to other neurons or muscles, then it will not be able to properly function. In Fred’s case his neurons could not send signals to other neurons or muscles, which lead to him experiencing numbness, tingling, and pain as well as weakness and an inability to contract his muscles (flaccid paralysis).*

**Observations**

*After examining the data and answering the analysis questions above, describe interesting observations and patterns you believe are relevant to explaining the phenomenon. You can include both textual and visual observations in order to help organize the data from above. (Include at least 10 important pieces of data and evidence that will aid in your final explanation of the phenomenon below)*

Observations will vary from student to student

Example Observations Listed Below:

* The neuromuscular junction involves neurons and target cells
* The target cells could be other neurons or muscle cells
* The neuromuscular junction has a presynaptic neuron and postsynaptic target cell (nerve or muscle cell)
* An action potential is sent down the presynaptic neuron as the first step in initiating a nerve or muscle action
* The action potential signals Ca2+ channels to open and release Ca2+ into the presynaptic neurons
* The Ca2+ causes neurotransmitters to be released from the presynaptic neuron
* When NTs are released into the synaptic cleft, they bind to ion channels on the target cell
* NTs binding to ion channels cause an influx of ions into the target cell which leads to an action potential in the target cell (i.e. nerve or muscle cell)
* The postsynaptic action potential causes either a nerve or muscle response
* A normal neuromuscular junction sequence goes from presynaptic action potential to NT release to postsynaptic action potential
* This would be the efferent pathway because the brain sends signals to efferent neurons to cause target cells to respond appropriately
* The afferent pathway is the information going to the brain to provide information necessary to initiate an appropriate response
* Botulinum toxin affects the NMJ
* NTs are NOT released, because the toxin interferes with proteins that allow the NT vesicles to dock on the presynaptic membrane and release their contents (i.e. acetylcholine)
* The toxin prevents the NTs from being released, which means there won’t be any acetylcholine available to bind to the ion channel receptors on the post synaptic target cells
* If this happens on a muscle cell then the muscle will not receive signals from NTs, which means it cannot contract, because there will not be any initiation of an action potential
* Fred was infiltrated with clostridium botulinum which is the bacteria that produces botulinum toxin
* Fred’s wound was the entry site for the bacteria
* The toxin disrupts normal homeostasis of afferent and efferent communication in the nervous system (CNS)
* By blocking the release of NTs the toxin prevents efferent signals from fully reaching the target cells
* If Fred did not receive medical attention, flaccid paralysis of his respiratory muscles could have occurred, which would have led to an inability to breath and survive

**Explanation**

*Based on your observation and analysis question responses, please provide an answer to the driving question in the box below. Remember to include data from above as evidence, important ideas from the previous unit, and the concept of homeostasis in your response.*

**Driving Question(s)**

*Why did the botulinum toxin cause nerve complications and mild flaccid muscle paralysis in Fred? If Fred did not receive* *medical attention immediately, would he have survived? Why or why not?*

Explanations will vary from student to student

A detailed example explanation is provided below:

After Fred was infiltrated by the bacteria clostridium botulinum, he was introduced to the botulinum toxin. This toxin is quite dangerous when it is produced in the human body, and it causes botulism. Botulism causes symptoms such as nerve dysfunction and muscle paralysis. In Fred’s case, his normal nerve and muscle homeostasis was disrupted. Normally the CNS functions through afferent and efferent pathways. Afferent pathways allow signals from either external or internal stimuli to travel to the brain to be interpreted appropriately. After interpretation, the brain decides what type of response will be appropriate to send along efferent pathways to react to the stimuli and maintain homeostasis. An example of an efferent pathway would be the NMJ, and under normal circumstances the NMJ functions by sending action potentials down the presynaptic neuron, which leads to a release of NTs into the synaptic cleft, then the NTs bind to ion channels on the target cells (postsynaptic cell) which generates and action potential (response) in the target cell (nerve to muscle).

In Fred’s case there is a disruption in the NMJ due to the botulinum toxin. The toxin can be found in the presynaptic neuron, which means the presynaptic release of NTs is affected. The toxin is capable of preventing the release of the NT acetylcholine from the presynaptic cell, by cleaving the docking proteins for the NT vesicles. This NT release blockage leads to inactive ion channels, because there is no acetylcholine available to bind to postsynaptic receptors (i.e. sodium ion channels). The lack of NT binding, means there is no action potential generated in the target cell, ultimately leading to nerve dysfunction and flaccid muscle paralysis.

If Fred did not receive medical help, there is a good chance he would not have survived. Since the botulinum toxin affects nerves and muscles this could lead to lethal consequences. The main cause of death from the toxin is due to flaccid muscle paralysis of the respiratory muscles. When this happens, the person affected by the toxin, will not be able to breath properly and won’t survive. Fred was able to get help before the toxin caused serious muscle paralysis and permanent nerve damage.