

# Unlucky Chucky and Toxins of the Neuromuscular Junction

by  
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## Introduction

The neuromuscular junction (NMJ) is the site of communication between the nervous system and skeletal muscles. Every NMJ includes a presynaptic motor neuron and a postsynaptic skeletal muscle fiber. A variety of receptors, channels, and enzymes associated with the NMJ have been targets for a striking number of naturally occurring toxins. Many of these toxins have been critical in deciphering the physiology of the NMJ, the relationships between the autonomic and somatic branches of the nervous system, and have been fundamental in the generation of clinically relevant drugs. In this case study, we will examine three toxins that act at the NMJ to help reinforce understanding of NMJ physiology.

We will start with a review of the NMJ that focusses on the transmission of an action potential from the pre-synaptic neuron through the release of acetylcholine (ACh) to the reception of the impulse by the nicotinic acetylcholine receptor (nAChR) and the continuation of the endplate potential along the sarcolemma and the removal of acetylcholine from the synaptic cleft.

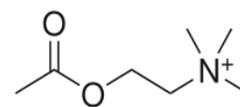


Figure 1. Acetylcholine.

## Exercise 1

Describe the structure and/or action that is identified by each of the seven labels of the schematic of the neuromuscular junction in Figure 2.

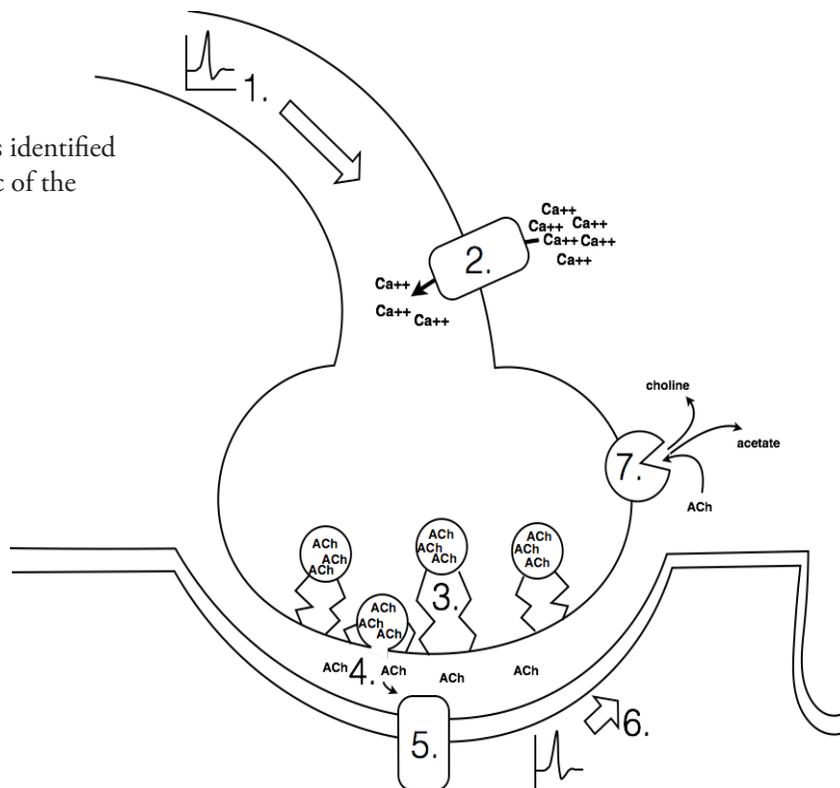


Figure 2. Diagram of the neuromuscular junction.

## Part I – Curare

Our story begins with Charles, a man who was around 40 years of age, 6 foot tall and weighed approximately 200 pounds. His friends called him “Unlucky Chucky” because of his unusual tendency to find himself in unfortunate and often life threatening situations. Chucky had decided to go with his good friend Melody on a restorative vacation to an eco-spa, a health resort focusing on natural healing products with low ecological impact, in the rain forests of Colombia.

Chucky and Melody were perusing the list of activities that could be experienced at the eco-spa when they noticed that a demonstration of local culture was about to begin in the outskirts of the resort.

“That demonstration looks like a lot of fun!” exclaimed Melody. “The brochure describes it as ‘a whirlwind of exciting culture, from dancing to native dart hunting techniques.’”

“I’ve always wondered how dart hunting works,” Chucky replied.

And so the two ventured to the demonstration, making it just in time before the show began. They watched with interest as the demonstrators danced, sang and described unique elements of the local culture, although it wasn’t until the emcee began mentioning that the dart hunting demonstration would be next that they were truly excited.

“Please everyone, no flash photography, this technique needs utmost silence so that our hunter won’t misfire.” The emcee was very explicit in his warning to the audience as the hunter prepared a blowgun with a special dart. “This dart is tipped with curare, a potent compound from a local plant that can stop a charging jaguar in its tracks by interfering with the animal’s muscles and nervous system, so please be careful!”

Chucky and Melody shifted to the edge of their front row seats as the hunter aimed his blow gun at a small animal only a few feet away from them. The hunter took a large breath inward as he prepared his attack; suddenly there was a bright flash! The hunter, momentarily blinded, then misfired his dart and hit Chucky in the neck, piercing his jugular vein. Chucky was stunned by the impact and quickly experienced difficulty breathing and an inability to talk or move the side of his body the dart had hit. No longer able to stand, Chucky fell to the ground.

### Questions

Use library and other Internet resources to answer the questions below in your groups. Make sure to include citations for the resources that you use.

1. What is curare? What is the active ingredient in curare?
2. Where does d-tubocurarine act at the biochemical level?
3. Why did Chucky fall to the ground and show an inability to talk or move the side of his body? What will happen if Chucky does not receive treatment quickly?
4. Spend some time in your group discussing what characteristics a drug treatment would need to have to reverse the symptoms associated with poisoning by curare. Write down two of your best ideas to share with the class.

## Part II – Sarin

Melody knew exactly what was happening to Chucky as he clutched his neck. Having a fair amount of information about the neuro-muscular junction, she knew that curare only affected skeletal muscles, and as long as his diaphragm was working, her good friend should be fine. Nonetheless, witnessing Chucky laying motionless on the ground made Melody nervous. “Medic!” she shouted.

Quickly one of the medical staff was at Chucky’s side ready to administer an injection of an unknown clear liquid. Melody sighed in relief when she watched the needle plunge into one of Chucky’s veins.

“What are you injecting?” Melody asked with curiosity

“It’s a derivative of a natural plant called the Calabar bean. The drug is called physostigmine,” the medic replied curtly.

Melody quickly grabbed her phone and read the Wikipedia article on physostigmine. While reading she noticed that Chucky was still not moving and said, “It’s not working. Why did you use physostigmine? The Internet says that it’s relatively weak compared to sarin gas, so why not use that?”

Shocked at the request, the medic wanted to ignore her question but felt he had to reply, saying simply, “Nobody should *ever* use sarin gas as a therapeutic. Just wait a bit and he will recover.”

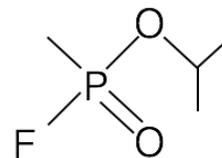


Figure 3. Sarin gas.

### Questions

1. What is the biochemical target of physostigmine and sarin gas?
2. What do these chemicals do to the target and how would this affect signaling at the NMJ?
3. Why should sarin *never be used as a therapeutic* to counteract the effects of curare poisoning even though it has the same target as physostigmine? (*Hint*: think of the type of interaction it has with the target.)

## Part III – Botox

Following his recovery from being hit by the poisoned dart, Chucky and Melody decided to take advantage of the free spa day that was given to them as compensation for their unfortunate experience. They were walking along the hallways of the spa when Chucky noticed a brightly colored sign exclaiming, “Botox is Back! ½ off all restorative Botox treatments!”

Upon seeing the sign, Chucky was excited. “Wow! I could totally look younger if I were to get some Botox! Let’s do it, Mel!”

Melody’s brow furrowed as she read the sign. “What? Are you crazy? You just recovered from being poisoned, why would you want to be poisoned again?”

“Quit being so melodramatic Melody; it’s been approved by the FDA, it can’t be poison,” Chucky reasoned.

“Well, you know it also wears off after a few months, so you’d have to get more,” Melody replied.

### Questions

1. What is Botox?
2. Where does botulinum toxin type-A act at the biochemical level?
3. Is Chucky correct about Botox being poisonous? Explain.
4. Is Melody also correct about the duration of effects of Botox? Explain.



## Conclusion

Following their brief discussion about the idea of getting a Botox treatment, Chucky figured it would be safest for him to get a massage instead. Chucky and Melody had a relatively relaxing time during the rest of their vacation; that is, until their trip to the airport—but that’s a different story...

### Exercise 2

Revisit Figure 2 from the beginning of this case study. Now draw your own version of a neuromuscular junction indicating where d-tubocurarine, botulinum toxin, and sarin/physostigmine would act.

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