Case study: Malignant hyperthermia

Learning objectives:

1.1.1 Define the study of Anatomy and Physiology and describe the hierarchical organization of the human body into chemicals, cells, tissues, organs and systems.
4.1 Describe the structure and functions of the animal cell.
8.3.2 Describe the gross anatomy of a muscle organ and the microscopic anatomy of a muscle fiber.
8.3.3 Describe the neuromuscular junction.
8.4.1 Outline the sequence of events between the arrival of a nerve impulse and contraction of a muscle fiber.
8.6.2 Compare aerobic and anaerobic respiration in muscle cells and state the biochemical causes of muscle fatigue.

Consider reviewing the following topics:

Metabolism, anatomy of a muscle organ and muscle fiber, neuromuscular junction, muscle contraction, and muscle cell metabolism. Consider reviewing the following resources: “The Muscular System” lecture notes (slides 1- 53) and “The skeletal muscle sarcomere” and “Skeletal muscle anatomy and contraction” worksheets.

Introduction

Patient story:

Stephanie sustained a knee injury during a skiing accident on a school field trip. A collision with a friend caused a tear in her anterior cruciate ligament (ACL), leading to several months of physiotherapy. During a follow-up visit with her doctor, they discovered that the ligament had healed improperly, which was causing Stephanie some discomfort. The doctor outlined some possible solutions, including more physiotherapy or surgery. Surgery would allow doctors to replace the ligament to allow for proper healing, gaining a level of mobility similar to before the accident, and alleviating her pain. Given how young and active Stephanie was, she and her family chose to perform the surgery. The surgery would involve an autograft where a piece of a tendon would replace her ACL. Surgeries like this are commonplace in athletes who tear their ACL, and generally, there are no major complications involved with the procedure.

On the day of the surgery, an anaesthetic gas agent called sevoflurane was administered for the surgery, and everything seemed fine at the start. The surgery was scheduled to take around 3 hours, however, over the course of the first hour, Stephanie’s carbon dioxide output and heart rate slowly started to climb. Also, the nurses noticed that several of Stephanie’s muscles were unusually contracted. Near the end of the first hour, her body temperature had reached 41℃, and the anesthesiologist determined that immediate action was required and administered the drug dantrolene.

The anaesthesiologist suspects that Stephanie has malignant hyperthermia, something that she has only seen in textbooks. This disorder is normally caused by a mutation in the RYR1 gene. This gene codes for an active calcium channel called ryanodine receptor 1 that is found in the membrane of the sarcoplasmic reticulum (SR) of skeletal muscle (and absent in cardiac muscle). This channel is responsible for allowing calcium out of the SR during muscle contraction. In patients with malignant hyperthermia, a certain class of anaesthetics binds to this calcium channel, forces it open, and causes the perpetual release of calcium into the

sarcoplasm of the skeletal muscle cell as long as the anaesthetic is still bound. This causes the skeletal muscle to stay contracted and rigid. While remaining contracted, the muscle uses a lot of ATP (much like a muscle performing at peak-intensity). The muscle cell needs to replenish this ATP, and the appropriate metabolic processes need to occur.

Along with giving the calcium-channel inhibiting drug, dantrolene, the nursing staff applied a hypothermic blanket and administered pure oxygen. These interventions not only treated her symptoms but also the underlying biochemical cause of her symptoms. Dantrolene physically closes the calcium channel by outcompeting the anaesthetic and binding to the channel (the application of the hypothermic blanket and the administration of pure oxygen will be addressed in-class). Due to how fast the doctors and nurses were able to treat Stephanie's symptoms, some of the major complications associated with the disorder were avoided. Typically, if the symptoms of malignant hyperthermia are not treated quickly enough, patients can suffer from internal hemorrhaging and kidney failure.

The medical staff are quite relieved to hear about Stephanie's prognosis. Despite the trauma, there is no permanent damage to any organs, and Stephanie's doctor has ordered her to remain in the hospital for a couple of weeks for further monitoring. Stephanie's parents and siblings are especially elated. To their knowledge, there have been no family incidences of negative reactions to anaesthetic. Some time after the surgery, Stephanie finally wakes up.