ABSTRACT

A Review of Hyperkalemic Periodic Paralysis and Proposal of A Symptom Mitigation Tool

Aeleia Frances Hughes

Director: Dr. Rizalia Klausmeyer, PhD

Hyperkalemic Periodic Paralysis (HyperPP) is a disease caused by a mutation of the SCN4A gene (Weber et al., 1993). This gene codes for the alpha-subunit of the voltage-gated $Na_v1.4$ sodium channels found in skeletal muscle (George et al., 1993), which are essential to uniform muscle contraction (Weber et al., 1993). HyperPP manifests as episodes of flaccid muscle weakness, typically evident in the patient's first decade of life. (Statland et al., 2018a). A possible trigger for HyperPP attacks is dietary potassium intake (V. Sansone et al., 2008). The aim of this paper is to discuss the onset mechanisms of HyperPP and current treatment pathways, and to propose an application capable of tracking the nutrient data of food items, including potassium content, to help patients mediate their symptoms. To determine the efficacy of this novel management tool, a study should be completed 12 months after it is released for public use.

APPROVED BY DIRECTOR OF HONORS THESIS:

_____

Dr. Rizalia Klausmeyer, Director, Office of Undergraduate Research

APPROVED BY THE HONORS PROGRAM:

_____

Dr. Elizabeth Corey, Director

DATE: _____

A REVIEW OF HYPERKALEMIC PERIODIC PARALYSIS AND PROPOSAL OF A SYMPTOM MITIGATION TOOL

A Thesis Submitted to the Faculty of

Baylor University

In Partial Fulfillment of the Requirements for the

Honors Program

By

Aeleia Hughes

Waco, Texas

August 2020

TABLE OF CONTENTS

ACKNOWLEDGEMENTS

I would like to thank my thesis mentor, Dr. Rizalia Klausmeyer, for allowing me to pursue this topic for my honors thesis and her continued support throughout the project. I would also like to thank my reviewers, Dr. Rizalia Klausmeyer, PhD, Dr. Richard Sanker, PhD, Dr. Marty Harvill, PhD, Dr. Rabindra Kitchener, MD, and Dr. Lois Krousgrill, MD.

DEDICATION

To my wonderful family, my colleagues, and the patients who suffer from this disease.
Mom, I wish all patients could have a caretaker as amazing as you are.
Dad, this paper is just the first step to understanding this disease.
I will find a way to help you; please don't give up on me.
We will make it through this together.

CHAPTER ONE

Introduction

An Overview of Hyperkalemic Periodic Paralysis

Hyperkalemic Periodic Paralysis (HyperPP), a condition characterized by episodes of flaccid weakness, affects approximately 1 in every 200,000 people (Statland et al., 2018a). This disease is the result of a genetic mutation, and as such, symptoms can either be present from birth, or acquired later in life. Although the ways in which HyperPP is acquired have not been determined, its genetic expression is relatively understood. The specific mutation that causes HyperPP is inherited in an autosomal dominant fashion. This means that if a heterozygous, affected individual has children with an unaffected, homozygous recessive individual, there is a 50% chance that each of the children will inherit HyperPP (Weber et al., 1993).

As its name implies, HyperPP presents itself in the form of attacks rather than constant weakness. Along with flaccid weakness, patients typically experience the absence of deep tendon reflexes in at least one limb during an attack. These attacks are usually preceded by a trigger. A list of possible triggers can include, among others, intake of dietary potassium, rest after exercise, fasting, exposure to cold, emotional stress, or pregnancy. The manifestation of HyperPP is usually accompanied by the presence of hyperkalemia during attacks, though this is not always the case (V. Sansone et al., 2008).

Hyperkalemia is a term that refers to a situation in which the level of potassium in the body is higher than 5.5mmol/L, the maximum concentration that is considered normal. (Shrimanker & Bhattarai, 2020). This has severe effects on the function of the nervous

system, muscular system, cardiovascular system, and other biological processes essential to the health and wellbeing of the patient. In fact, conditions that affect the serum concentration of potassium can be rapidly fatal (Ellison et al., 2016) due to potassium's effect on the cardiovascular system. Cardiac arrhythmias occur when the heart is unable to regulate its rhythm. Arrhythmias are often unsustainable and have the potential to be fatal. Hyperkalemia is the electrolyte disorder that is the most lethal and causes the most cardiac arrhythmias (Ueda et al., 2019). Fortunately, the levels of potassium in the blood of HyperPP patients rarely reach cardiotoxic levels (Weber et al., 1993).

Potassium is an electrolyte, commonly an intracellular ion, that is filtered out of the blood by the kidneys. The pressure difference created by blood flowing through the glomerulus allows potassium ions to leave the bloodstream. The kidney reabsorbs potassium through the walls of the proximal convoluted tubule and the ascending loop of Henle, while it secretes potassium through the wall of the distal convoluted tubule (Shrimanker & Bhattarai, 2020). Since the primary mode of excretion of potassium is via the kidneys, hyperkalemia is a common symptom of impaired kidney function (Ellison et al., 2016). However, barring contraindications, this excretion system can be targeted by pharmaceuticals to alleviate hyperkalemia.

Symptoms of HyperPP are more likely to be apparent when considering the nervous system and muscular system, and these give rise to varied clinical presentations across the patient population. For this reason, it is imperative to establish set diagnostic criteria. Differential diagnosis of HyperPP is dependent on two categories of data: suggestive findings and diagnostic testing.

Suggestive findings are symptoms which, while individually not capable of indicating a diagnosis of HyperPP, can be combined with each other and diagnostic testing results to establish a diagnosis. Although all possible symptoms are not likely to occur in each patient, any number of them may be clinically present, making patient history an important indicator of HyperPP. For example, presentation of episodes of flaccid muscle weakness manifesting in the first decade of life in a patient's history is a strong suggestive finding of HyperPP (Simkin & Bendahhou, 2011). In fact, symptoms will begin for approximately 50% of patients before they are 10 years old. (Statland et al., 2018a). Usually, the patient will have at least one affected family member, but a lack of HyperPP in a patient's family history does not preclude its diagnosis, because de novo mutations have occurred. Another suggestive finding Is the absence of cardiac arrhythmias and muscle weakness between attacks, indicating that a patient's potassium levels are likely normal between attacks, as well. Hyperkalemia and elevated creatine kinase usually occur during an attack, but not in all cases (Weber et al., 1993).

Electromyography (EMG) is a diagnostic tool that is used to elucidate evidence of changes in the excitability of muscle fiber due to a genetic mutation (Statland et al., 2018a). Myotonia can be a symptom of HyperPP and is the result of increased membrane excitability. Myotonia presents as muscle stiffness, which can occur between attacks. Typically, the myotonia will increase as an attack begins, but dissipate completely during events of total paralysis. In patients with HyperPP, myotonia usually does not restrict normal muscle movement. If an EMG detects myotonia in the muscle tissue, a diagnosis of HyperPP is supported (Jurkat-Rott & Lehmann-Horn, 2007). Myotonia is illustrated using needle EMG by a pattern of positive sharp waves (Statland et al., 2018a). EMG

identified myotonia suggests a diagnosis of HyperPP and is indicated in approximately 75% of patients, though not all of these will display myotonic symptoms (Venance et al., 2006).

Diagnostic testing refers to specific laboratory and clinically based tests that are capable of providing disease specific results, strongly indicating the presence of a particular condition. The diagnosis of HyperPP is confirmed by a genetic test that inspects the SCN4A gene. The tests used to survey the gene in question will indicate the position of the defect, regardless of whether the mutation was inherited or acquired later in life. Single-gene testing requires a specific gene to be sequenced and subsequently analyzed for a mutation. This type of testing is used if there is only one gene of interest for a given test. Multigene panels involve sequencing several genes of interest and analyzing them for mutations. There are more comprehensive genomic tests, which can be used in the event that single-gene and multigene testing fail to identify the mutation; however, the specifics of these procedures are outside the scope of this paper (Weber et al., 1993).

Another category of diagnostic tests, provocative tests, demonstrate a patient's physiological response to an increase in serum potassium. These tests are used to eliminate diagnostic uncertainty in the absence of genetic testing or ability to measure serum potassium during an attack. There are three types of provocative tests: the classic provocative test, the alternative provocative test, and the local provocative test. The classic provocative test involves the intravenous administration of potassium (2-10g) to the point of inducing an attack. The serum potassium concentration, as well as muscle strength, is measured every 20 minutes. If the patient experiences an attack, the diagnosis of HyperPP is confirmed. A contraindication for this test is the presence of hyperkalemia or inadequate

renal or adrenal function. Alternative provocative tests use exercise, rather than intravenous administration, to increase a patient's serum potassium content. Patients exercise for 30 minutes on a bicycle, increasing their heart rate to 120-160 beats per minute. HyperPP is indicated if their serum potassium level increases during exercise, decreases after exercise, and then increases, again, approximately 20 minutes after they stop exercising. The diagnosis of HyperPP is confirmed if the patient observes absolute rest for that time period between exercise and the second increase in serum potassium levels, and an attack occurs. Finally, the local provocative test uses measurements of compound muscle action potentials (CMAP) in response to exercise to confirm a diagnosis of HyperPP. If HyperPP is clinically indicated, the increase in CMAPs will be greater than normal for the first few minutes of exercise. This will be followed by a greater than normal decline, which will be most rapid in within the first 20 minutes of exercise. However, the results of local provocative tests may not be exclusively indicative of HyperPP (Weber et al., 1993).

There are treatment options for HyperPP, but there is no known cure. In fact, due to the difficulty obtaining the correct diagnosis, patients are sometimes treated in ways that exacerbate their symptoms rather than alleviating them (Iaizzo et al., 1995). The long-term effects of HyperPP, regardless of the efficacy of the observed treatment protocol in the short-term, often include progressive vacuolar myopathy (Hayward et al., 2008). Muscle biopsies can be used to identify the presence of vacuolar myopathy, caused by progressive degeneration of the transverse tubular system and the sarcoplasmic reticulum found in myocytes. As determined by the underlying missense mutation, HyperPP can lead to permanent weakness (Jurkat-Rott & Lehmann-Horn, 2007).

HyperPP is a condition that is debilitating, painful, and potentially fatal. Patients are often misdiagnosed and do not receive the help that they need because the diagnostic criteria are not standardized. The variety of symptoms and missense mutations displayed by individual patients makes a universal treatment protocol impractical, but highly individualized plans require the aforementioned correct diagnosis. A study conducted by Charles et al., reported that it took an average of 19.4 years and four different physicians for patients in the study to receive the correct diagnosis of HyperPP (G. Charles et al., 2013). Without the correct diagnosis, access to the appropriate pharmaceuticals is restricted, leaving patients with undiagnosed or misdiagnosed HyperPP unable to control their symptoms. However, since HyperPP generates symptoms due to an electrolyte imbalance, it may be possible to manage the symptoms of the disease through diet modification. The working hypothesis of this paper is that nutrition can be used to effectively and efficiently alleviate the symptoms of HyperPP.

CHAPTER TWO

Neuromuscular Physiology

An Overview of the Neuromuscular System

If HyperPP is to be understood, one must first have a functional understanding of the nervous system. The nervous system is comprised of two main regions: the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS is made up of the brain and the spinal cord, while the PNS refers to the segments of the nervous system that transmit signals between the central nervous system and the rest of the body. The PNS is also comprised of two main divisions: the autonomic nervous system (ANS) and the somatic nervous system (SNS) (OpenStax, 2013a).

The ANS is responsible for regulating involuntary processes within the body, which it does through the use of neurotransmitters and receptors. The afferent limb of the ANS carries information to the CNS from the body, while the efferent limb carries information from the CNS to the rest of the body (Benarroch, 2007). The efferent limb is influenced by the sympathetic and parasympathetic nervous systems. The sympathetic nervous system is responsible for the "fight or flight reflex". The sympathetic nervous system uses catecholamine hormones to communicate with tissues in the body, primarily norepinephrine; however, in some cases, it uses epinephrine. Catecholamines represent a class of compounds that are derived from the aromatic amino acid, phenylalanine. The parasympathetic nervous system, conversely, is responsible for returning the body to a resting state after sympathetic activation. The effects of the parasympathetic nervous system on tissues, therefore, counteracts those of the sympathetic nervous system. For

example, instead of dilating the pupils, which would be the result of the activation of the sympathetic nervous system, activation of the parasympathetic nervous system would cause the pupils to constrict (Bankenahally & Krovvidi, 2016).

The SNS is responsible for regulating voluntary movement of the body, which is accomplished via the skeletal muscles. The SNS contains both afferent nerves (sensory), and efferent nerves (motor). A neuromuscular junction (NMJ) is required to convert the electrical signal transmitted by the efferent nerve to a chemical signal that will cause the muscle tissue to contract (Akinrodoye & Lui, 2020).

The individual nerves that make up the nervous system transmit signals from one part of the body to another. However, this process is only possible if a resting membrane potential is maintained. A resting membrane potential is established by a concentration gradient of ions across the membrane of a neuron. The sodium concentration on the extracellular side of the neuron is approximately 10 times higher than the sodium concentration on the intracellular side of the neuron. Observing the laws of diffusion, the sodium ions on the extracellular side the neuron, where it is more concentrated, will naturally attempt to enter the neuron in order to equilibrate the concentration of sodium on both sides of the membrane. The concentration of potassium ions on the intracellular side of the neuron is more than 20 times higher than the extracellular concentration. Like the sodium ions, the potassium ions will naturally attempt to equilibrate the concentration across the membrane. The voltage established across the membrane due to this concentration gradient, usually about -70mV, is called the resting potential (Burdusel C, 2006).

The resting potential is maintained by the sodium-potassium pump, also known as the sodium-potassium-ATPase. This is an example of active transport, requiring ATP, because the sodium-potassium pump moves ions against their concentration gradient. When the neuron is not actively responding to a stimulus, the intracellular side of the cell membrane has a slightly more negative electric potential than the extracellular side. The intracellular side of the neuron is more negative because the sodium-potassium pump moves three sodium ions out of the cell, followed by two potassium ions into the cell for every ATP used. Though both sodium and potassium are alkali metals, and therefore exist in solution as monovalent cations, the resting potential is negative on the intracellular side of the neuron. This is because for every three positive ions that are removed, only two take their place. That is a net gain of a negative one charge on the intracellular side of the cell and a positive one charge on the extracellular side of the cell every time the sodium-potassium pump goes through one cycle (Burdusel C, 2006).

The resting membrane potential is also maintained by ion channels, located in the cell membrane. These are transmembrane pores that permit a particular ion to cross the membrane to partially alleviate the concentration gradient. Ion channels employ electrochemical exclusion to increase their specificity. This means that a cation channel will have negatively charged amino acids incorporated into the pore, preventing anions from traveling through it. The opposite is true for anion channels: they will have positively charged amino acids incorporated into the pore to prevent the passage of cations. Some ion channels are also size specific. The pore of these channels are approximately equivalent to the diameter of the designated ion (OpenStax, 2013b).

There are four main categories of gated channels: ligand-gated channels, mechanically gated channels, voltage-gated channels, and leak channels. Ions are unable to move freely through these channels because each of them requires a stimulus to open. Ligand-gated channels open when a specific signaling molecule, a neurotransmitter, binds to the receptor on the extracellular side of the neuron. The mechanically gated channel requires a disturbance of the cell membrane to open. A voltage-gated channel requires a decrease in the negative voltage on the intracellular side of the membrane to open. Finally, a leakage channel opens randomly. These channels do not require or respond to a particular event, but they contribute to membrane excitability (OpenStax, 2013b).

The transmission of electrical signals throughout the nervous system is due to the propagation of action potentials. An action potential begins with the depolarization phase. First, sodium ions enter the neuron, causing the membrane to become less negative. Eventually, the voltage will reach an adequate potential to open the voltage-gated sodium channels, which is known as the threshold voltage. Action potentials occur in "an-all-or-nothing" manner, meaning that if the threshold voltage is not reached, the process will be stopped and the resting membrane potential will be restored. However, once the threshold is reached, the voltage-gated sodium channels open, allowing sodium ions to flow into the cell more freely. Once the neuron has reached peak depolarization, the voltage-gated sodium channels are closed, preventing the influx of sodium (Grider & Glaubensklee, 2020).

The next phase of the action potential is the repolarization phase. The voltage-gated potassium channels are activated at the same time and by the same mechanism as the voltage-gated sodium channels, but they activate more slowly. So, the voltage-gated

potassium channels open just as the voltage-gated sodium channels are inactivated, causing the efflux of potassium ions to coincide with the cessation of the influx of sodium ions. Since the net intracellular charge progressively decreases, the membrane potential approaches its resting voltage. When the membrane potential decreases enough that it is below the threshold voltage, the voltage-gated potassium channels and the voltage-gated sodium channels close. Because the voltage-gated potassium channels remain open for a longer period of time than is necessary to reestablish the resting membrane potential, a hyperpolarization phase is observed (Grider & Glaubensklee, 2020). This is corrected through the continued activity of leak channels and the sodium potassium pump (OpenStax, 2013b, p. 4).

An action potential travels down an axon through a process called conduction, which is possible due to the properties of sodium channels. First, the passive spread of membrane depolarization occurs, resulting in regional depolarization. However, due to the refractory period, the time in which voltage-gated sodium channels remain inactive after opening, and the hyperpolarization of the membrane, the action potential can only travel downstream. Thus, an action potential is unidirectional toward the axon terminus. The speed of neural conduction is increased when the axon is coated in a myelin sheath, which is produced by glial cells. The gaps between the myelin membrane units are called the nodes of Ranvier, which are the only locations along the axon that are capable of facilitating the transfer of ions required to maintain an action potential. The conduction of an action potential along a myelinated axon involves jumping from node to node and occurs much more quickly than the conduction of an action potential along an unmyelinated axon (Lodish et al., 2000).

When an action potential reaches the axon terminus of a motor neuron, it triggers the voltage-gated calcium channels to open, allowing calcium to enter the cell. This influx of calcium causes the vesicles containing the neurotransmitter acetylcholine to fuse with the presynaptic cell membrane, releasing their contents into a space between the motor neuron's axon terminus and the endplate of the skeletal muscle fiber called the synaptic cleft. The endplate contains acetylcholine receptors that, when bound by two acetylcholine molecules, changes shape and stimulates the muscle cell to allow the simultaneous gain of sodium ions and loss of potassium ions. If there are enough vesicles released from the presynaptic cell, meaning the axonal action potential was strong enough, the resulting endplate potential will exceed the threshold and cause muscle fiber contraction (Arrowsmith, 2007).

Skeletal muscle has a very different structure from nervous tissue. Muscle fibers are predominantly multinucleated, striated cells that "span the length of the muscle". Each skeletal myocyte is surrounded by a membrane called the sarcolemma, which is comprised of the plasma membrane and polysaccharides that are capable of binding to tendon tissues. The sarcolemma is also the site of motor neuron innervation (McCuller et al., 2020). An extension of the sarcolemma is the transverse tubular system, which carries action potentials across the muscle to individual muscle fibers and makes coordinated muscle contraction possible (Braithwaite & Al Khalili, 2020).

Muscle fibers are made up of many myofibrils, composed of thick filaments, thin filaments, and structural proteins. The thick filaments are made of the protein myosin and the thin filaments are made of the protein actin. Thin filaments contain myosin binding sites along the actin filament, which are covered by the fibrous protein tropomyosin with

bound troponin when intracellular calcium levels are low (Braithwaite & Al Khalili, 2020). The arrangement of thin filaments and thick filaments results in the characteristic striated pattern of skeletal muscle but is also responsible for its contractile ability. The contractile unit of a myofibril is called a sarcomere. The space between the end points of a sarcomere, the Z line, are where the thin filaments anchor for support. In the middle of the Z lines, an imaginary M line marks the point toward which the sarcomere contracts. The thick filaments are found in the H band, which is defined as the space between the M line and the beginning of the thin filament to either side. The portion of the sarcomere that features overlapping actin and myosin, along with the segment designated as the H band, is called the A band. Finally, the I band refers to the segment of the sarcomere that exclusively contains thin filaments and is the terminal region of two longitudinally adjacent sarcomeres. When a muscle contracts, the H band and the I band shorten, while the A band remains unchanged (McCuller et al., 2020).

Though skeletal muscle and nerve tissue differ greatly in their structure, under normal conditions, they communicate effectively to generate a motor response. After a sufficient endplate potential has been generated, an action potential is induced in the sarcolemma membrane that covers the muscle cell. The transverse tubular system, which is dependent on the action of voltage-gated $Na_v1.4$ sodium channels, conducts the action potential from the endplate along the muscle to the tendon. Depolarization occurs when the voltage-gated $Na_v1.4$ sodium channels open, allowing sodium ions to enter the cell. Rectifier potassium channels, which allow potassium to leave the cell, are delayed in their response to activation like the voltage-gated potassium channels in the nervous system. The rectifier potassium channels begin to establish the repolarization phase, but the

chloride channels quickly take the primary role in repolarization. Chloride channels allow chloride ions to enter the transverse tubular system, decreasing the membrane potential and mitigating the effects of a phenomenon exclusive to skeletal muscle action potentials, afterdepolarization. Afterdepolarization is comprised of two stages, an early phase and a late phase, which are differentiated by the ionic current on which they rely. The early phase is initiated by the depolarization of the transverse tubular system, while the late phase is dependent on the increasing concentration of potassium ions in the transverse tubular system. Chloride ion influx stimulates the influx of potassium ions into the cell, relieving the depolarization state of the transverse tubular system. (Simkin & Bendahhou, 2011)

The depolarization of the transverse tubular system causes it to undergo a conformational change, stimulating the release of calcium ions from the sarcoplasmic reticulum into the muscle fiber. This increase in the intracellular concentration of calcium ions allows troponin to bind free calcium ions and induce a conformational change in troponin, thereby enabling it to move tropomyosin off of the myosin binding site. Since myosin has no bound adenosine triphosphate (ATP), it binds to the free myosin binding site on the actin filament (Braithwaite & Al Khalili, 2020). When the myosin head does bind ATP, it induces a conformational change that causes the myosin head to release the actin filament. The ATP is hydrolyzed, which re-cocks the myosin head and causes it to move down the thin filament toward the Z line of the sarcomere. If the intracellular concentration of calcium is still at favorable levels, then the myosin head will bind to actin, again, creating a complex known as a cross-bridge. When the ADP and inorganic phosphate group are released from the myosin, a power stroke is generated wherein the myosin head moves toward the M line, pulling the actin filament with it. The displacement

of the actin filament shortens the sarcomere, causing muscle contraction (McCuller et al., 2020).

The contractile function of muscle is dependent on the ability to the nervous system to effectively communicate an action potential to the muscular system and the efficacy of the muscle to react to that action potential.

CHAPTER THREE

The Biological Basis of Hyperkalemic Periodic Paralysis

An Investigation of Causes, Symptoms, and Treatment Options

HyperPP is caused by a missense mutation in the SCN4A gene, located on chromosome 17q23-25 (Sasaki et al., 1999). With 24 exons and 23 introns, the SCN4A gene contains approximately 32.5 kb of DNA that encodes the alpha-subunit of the voltage-gated $Na_v1.4$ sodium channels found in skeletal muscle (George et al., 1993). A functioning voltage-gated $Na_v1.4$ sodium channel is essential to uniform muscular contraction because it directly impacts the ability of the muscle to generate and propagate an action potential (Weber et al., 1993).

The alpha-subunit of the voltage-gated $Na_v1.4$ sodium channel is comprised of "four homologous domains, and each domain has six transmembrane segments" (Simkin & Bendahhou, 2011), and it is responsible for the "properties of ion selectivity, voltage sensitivity, pharmacology, and binding characteristics for endogenous and exogenous ligands" (Weber et al., 1993). The alpha subunit's pore forming function is dependent on the beta subunit's regulatory function (*SCN4A - Sodium Channel Protein Type 4 Subunit Alpha - Homo Sapiens (Human) - SCN4A Gene & Protein*, n.d.). This pore-forming capability allows the voltage-gated $Na_v1.4$ sodium channel to permit sodium ions to enter the muscle cell (Weber et al., 1993).

The voltage-gated $Na_v1.4$ sodium channel cycles through three gating states, one open state and two closed states (Weber et al., 1993). When resting membrane potential is observed, the voltage-gated $Na_v1.4$ sodium channel is in its resting state. In the resting

state, the S4 segment is attracted to the intracellular side of the channel, keeping it closed (Pan et al., 2018). The voltage-gated $Na_v1.4$ sodium channel's S4 segments induce a conformational change in response to a change in voltage at the membrane, which leads to the activation of the channel (Simkin & Bendahhou, 2011). When the membrane potential changes, the S4 segment moves out of the channel, opening the pore "through a process known as electromechanical coupling" (Pan et al., 2018). After the voltage-gated $Na_v1.4$ sodium channel has been activated, it exists in its open state (Weber et al., 1993).

The inactivated state is different from the resting state in that it is unable to be stimulated for a given period of time. The voltage-gated $Na_v1.4$ sodium channel can be inactivated by two different mechanisms depending on the preceding conditions (Weber et al., 1993). The two mechanisms of inactivation in voltage-gated $Na_v1.4$ sodium channels are fast-inactivation and slow-inactivation. Fast inactivation is understood to follow the hinge-lid model, which postulates the inactivation of the channel via a mechanical blockage that rapidly stops the influx of sodium ions. Currently, this "inactivation particle" is thought to be composed of the amino acids Isoleucine, Phenylalanine, and Methionine. Typically, this type of inactivation corresponds with short periods of depolarization. Slow inactivation occurs when cells are depolarized for longer periods of time. This type of inactivation is thought to function regardless of the presence of fast inactivation (Lehmann-Horn & Jurkat-Rott, 1999). Slow inactivation permits changes in membrane potential across a duration of time to affect membrane excitability rather than reacting to a single action potential (Takahashi & Cannon, 1999).

Mutations in the SCN4A gene can lead to structural changes in the alpha subunit of voltage-gated $Na_v1.4$ sodium channels, which can affect the inactivation mechanisms

(Green et al., 1998). Mutations associated with HyperPP are classified as "gain-of function mutations" because they inhibit complete inactivation, resulting in a constant functioning state. Continuous influx of sodium ions can result in either increased or decreased membrane excitability, depending upon the level of depolarization experienced by the cell. A lower level of depolarization permits recurrent action potentials, leading to increased membrane excitability, which can cause myotonia. However, increased depolarization levels can lead to an decrease in membrane excitability, resulting in paralysis (Kim, 2014).

Myotonia is a condition in which repeated, muscle generated action potentials continue to be observed after stimulation from the motor neuron at the neuromuscular junction has ceased (Khogali et al., 2015). This increase in membrane excitability is thought to arise from an increase in the concentration of cations in the transverse tubular system (Jurkat-Rott et al., 2010). Previous studies have determined the cause of HyperPP with myotonia to be the segment of the SCN4A gene that codes for the alpha subunit of the voltage-gated $Na_v1.4$ sodium channels, specifically the loci that encodes the portion of the channel that is responsible for sensitivity to tetrodotoxin (TTX) (Lehmann -Horn et al., 1991).

In patients with HyperPP and myotonia, the presence of electrical myotonia does not necessarily indicate clinically observable myotonia. Between 50 - 75% of patients with HyperPP present electrical myotonia, while less than 20% of patients are affected by clinical myotonia (Venance et al., 2006). Electrical myotonia refers to the "spontaneous muscle fiber discharge" in the range of 20-80 Hz elucidated via needle EMG testing. When the audio function is utilized, myotonic signals generate a "dive-bomber" sound. Clinical myotonia is demonstrated by a patient's inability to relax a muscle voluntarily (Hehir &

Logigian, 2013). When myotonia is clinically present, it can usually be alleviated by mild exercise or repetitive movements. This process is designated the "warm-up phenomena" because of the dissipation of symptoms after the muscle is repeatedly activated. Conversely, another type of myotonia is paramyotonia, which is characterized by an increase in symptom manifestation during exercise. Paramyotonia also occurs when the muscle is exposed to cold temperatures (Fontaine et al., 1996).

Patients with myotonia present symptoms to varying degrees. Some may exhibit only electrical myotonia, some may have clinically apparent myotonia, and others may experience a change in muscle bulk. Typically, patients that experience "moderate to severe generalized myotonia" demonstrate an increase in muscle bulk due to the hypertrophic effects of the myotonic contractions (Cannon, 2015). Patients that do not display myotonia between attacks are more likely to develop the progressive vacuolar myopathy associated with some of the genetic mutations that cause HyperPP (G. Charles et al., 2013).

Unlike myotonic symptoms, the paralysis experienced by patients with HyperPP is electrically silent. In order for this to occur, both the slow and fast inactivation mechanisms of some of the voltage-gated $Na_v1.4$ sodium channels in a muscle cell have to be disrupted. A small percentage of mutated channels that permit the constant influx of sodium ions will depolarize the membrane enough to result in membrane inexcitability (Ruff, 1994).

Essentially, due to the constant influx of sodium ions, the cell is depolarized for an extended period of time. The resulting voltage potential becomes more positive, causing the potassium ions in the cell to be released to alleviate the positive charge. The release of potassium ions, coupled with the cotransport of water with the sodium ions into the muscle

cell, leads to an increase in the serum concentration of potassium. Like an action potential, this cycle spreads throughout the muscle and is responsible for the weakness associated with HyperPP. The increase in serum potassium ions and the influx of sodium ions incompletely activate the sodium pump, which is capable of relieving the weakness if stimulated correctly (Jurkat-Rott & Lehmann-Horn, 2007).

Normally, the increase in extracellular potassium concentration triggers the slow inactivation mechanism of the voltage-gated $Na_v1.4$ sodium channels. However, some mutations of the SCN4A gene result in the disruption of the slow inactivation mechanism, which prohibits the channel from effectively entering its inactive conformation (Simkin & Bendahhou, 2011). Of the multiple pathogenic mutations in the SCN4A gene that can result in HyperPP, 75% of patients display T740M or M1592V (Venance et al., 2006) and T740M "alone accounts for 69% of pathogenic variants" (Weber et al., 1993). Both of these mutations affect the efficacy of voltage-gated $Na_v1.4$ sodium channel slow inactivation (Simkin & Bendahhou, 2011).

The clinical significance of HyperPP extends beyond the neuromuscular field into anesthesiology. The use of depolarizing anesthetic agents can have devastating ramification for patients with HyperPP. These medications, as well as potassium, anticholinesterases, and succinylcholine, along with opioids, have the potential to exacerbate myotonic tendencies, resulting in prolonged muscle contraction. In this case, it is possible to experience respiratory muscle stiffness, which can lead to complications with "intubation and mechanical ventilation" (Weber et al., 1993). The myotonia is worsened by other intraoperative occurrences such as "alterations of serum osmolarity, pH, and hypothermia-induced muscle shivering and mechanical stimulation" (Jurkat-Rott &

Lehmann-Horn, 2007). It is possible for patients to experience respiratory distress after emergence from anesthesia due to weakness of the respiratory muscles, which is compounded by drugs designed to reduce their respiration rate (Weber et al., 1993).

Treatment options for HyperPP can be classified as chronic or acute treatments. Chronic treatments can be further classified as those that reverse the periodic paralysis symptoms associated with HyperPP and those that alleviate myotonia. The list of medications discussed in this chapter was derived from the unpublished survey data of **a** study conducted by Frank Lehmann-Horn and Karin Jurkat-Rott that was provided as a reference in a 2013 study conducted by Charles et al.

One class of medications that is used to treat HyperPP is carbonic anhydrase inhibitors. There are several proposed mechanisms by which carbonic anhydrase inhibitors could affect patients with HyperPP; however, the precise mechanism of these drugs is currently unknown (Cannon, 2015). Carbonic anhydrase is an enzyme found in various tissues of the body, and is responsible for the interconversion of bicarbonate ions and carbon dioxide and water. Carbonic anhydrase inhibitors, therefore, impede the reabsorption of bicarbonate from the urine in the kidneys. Members of this class of drug also function as mild diuretics and increase the excretion of sodium, potassium, and bicarbonate from the kidneys. This decrease in serum bicarbonate can lead to metabolic acidosis (Vardanyan & Hruby, 2016).

One proposed mechanism for the efficacy of carbonic anhydrase inhibitors as a treatment for HyperPP is dependent on the resulting metabolic acidosis, because the decrease in pH coincides with a reduction in "susceptibility to periodic paralysis" (Cannon, 2015). Another possible mechanism involves the activating effect of carbonic anhydrase

inhibitors on calcium-activated potassium channels, which allow potassium ions to enter the muscle cell at a faster rate, reducing the extracellular concentration of potassium (Statland et al., 2018b). While either of these mechanisms is possible, they may not be mutually exclusive in their contribution to carbonic anhydrase inhibitor induced reversal or prevention of paralysis symptoms in patients with HyperPP (Jurkat-Rott et al., 2010). Essentially, carbonic anhydrase inhibitors have been shown to reduce the frequency and severity of attacks in patients with HyperPP when taken prophylactically (Cannon, 2015).

Currently, dichlorphenamide is the only drug that is FDA approved for the treatment of HyperPP and is paradoxically prescribed for patients diagnosed with HyperPP, as well as those diagnosed with Hypokalemic Periodic Paralysis (HypoPP). In its phase 3 testing, dichlorphenamide was determined to be safe for both patients with HyperPP and patients with HypoPP using "a randomized, double-blind, parallel-group, placebo-controlled" study design. However, while the study found that patients with HypoPP experienced significant decreases in paralytic attack frequency and attack severity, the HyperPP trials did not result in a significant change (Burge et al., 2016).

A study published in 2016 indicated that the frequency of attacks in HyperPP patients taking dichlorphenamide compared to those taking a placebo was five times lower, though one of the HyperPP trials still failed to achieve significance (Greig, 2016). Another study published in 2019 affirmed the efficacy of dichlorphenamide by noting the long-term reduction in symptom manifestation associated with its use for patients with HyperPP (Johnson et al., 2019). While dichlorphenamide is effective at reducing the symptoms of HyperPP, no significant changes in muscle strength or muscle mass are correlated with its use (V. A. Sansone et al., 2016).

While it is the only FDA approved treatment for HyperPP, dichlorphenamide is not the only carbonic anhydrase inhibitor available to treat HyperPP. Acetazolamide can also be used to prevent paralytic attacks (Statland & Barohn, 2013). Since they belong to the same class of drugs, it is likely that acetazolamide and dichlorphenamide exert their effects via a similar mechanism. Although, given the current incomplete understanding of the precise nature of this process, that cannot be stated with certainty.

The next classification of medications having the capability to reverse the symptoms of paralysis is thiazide diuretics. The preferred medication in this class is hydrochlorothiazide (Statland et al., 2018b), which inhibits the transport of sodium chloride across the wall of the distal convoluted tubule. To counteract this, the influx of sodium ions into the distal convoluted tubule, as well as the water that accompanies it, increases. This has a similar effect as the carbonic anhydrase inhibitor compounds because hydrochlorothiazide results in the increased excretion of potassium and bicarbonate in the urine (Herman & Bashir, 2020).

Loop diuretics act as a competitive inhibitor of the Na-K-2Cl cotransporter, which is located in the thick ascending limb in the nephron's loop of Henle. Inhibiting this enzyme precludes the reabsorption of sodium and chloride, in a mechanism similar to that of the thiazide diuretics. The increase in concentration of the urine causes an increase in water excretion. Since, without a specialized protein, the wall of the lumen of the nephron is largely impermeable to potassium ions, loop diuretics decrease the concentration of potassium in a patient's blood. Furosemide and Torsemide are examples of loop diuretics that were prescribed to patients with HyperPP.

Myotonia can be alleviated by some pharmaceutical interventions. The first classification of drugs that inhibit myotonia are known as antiarrhythmic medications. These drugs are capable of producing an antimyotonic effect that inhibits mutant channels more effectively than normal channels (Jurkat-Rott et al., 2010). The most notable of these medications, mexiletine, was found to be "the only antimyotonic agent with randomized controlled trail data to support its use" in a study published in 2014. Unfortunately, the same study noted that mexiletine lacked efficacy for some of the patients, while others developed side effects. Also, because mexiletine is no longer being manufactured in some countries, it is difficult to procure for patients and researchers, alike (Matthews & Hanna, 2014). In patients with HyperPP, administration of mexiletine is usually not enough to mitigate the symptoms (Weckbecker et al., 2000) because, although mexiletine can relieve myotonia, it does not reverse the weakness experienced by patients with HyperPP (Jurkat-Rott et al., 2010).

Mexiletine affects sodium channels to varying degrees, depending on their states of activity, in a process called "use dependence". Specifically, mexiletine binds to sodium channels when they are depolarized, preventing them from opening. When the cell repolarizes, mexiletine dissociates, leaving the cell in its inactive state (Singh et al., 2020). Mexiletine is speculated to bind inside the pore of the sodium channel in a location that would allow it to block the movement of ions if it were utilized (Catterall, 2012). By blocking sodium channels, mexiletine can also prevent the conjugation of action potentials, alleviating myotonia (Singh et al., 2020).

Other antiarrhythmic medications, such as flecainide and propafenone also inhibit sodium channels but, according to in vivo studies, they do so to a greater effect (Matthews

& Hanna, 2014). Although prescribing practices are outside of the scope of this paper, given their effect on sodium channels, flecainide and propafenone may warrant further investigation for use by patients with HyperPP to reduce the manifestation of symptoms. Finally, other classifications of medication function by inhibiting sodium channels; for example, muscle relaxants (such as orphenadrine) and anticonvulsants (such as carbamazepine) inhibit the sodium channels to exert their effect (Matthews & Hanna, 2014).

Due to the various clinical presentations that arise from the multiple possible mutations that can lead to HyperPP, treatment of acute symptoms is a highly individualized process. However, there are certain treatment options that generally apply to patients with HyperPP: mild exercise, inhalation of beta-2 agonists, and dietary considerations (Jurkat-Rott & Lehmann-Horn, 2007). The reason behind the therapeutic effect of mild exercise for patients with some forms of HyperPP was discussed in the preceding chapter, and dietary considerations will be examined in detail in the following chapter.

Beta-2 agonists induce serum hypokalemia due to the stimulation of a beta-2 adrenoreceptor that influences sodium-potassium ATPase, which moves extracellular potassium into the cell and releases intracellular sodium ions (Whyte et al., 1987). The commonly taken beta-2 agonist is salbutamol. Typically, salbutamol is inhaled in an aerosolized form, but tablets are available. Both forms of the medication are capable of acting prophylactically to prevent an attack of paralysis (Clausen et al., 1980). Not only is salbutamol capable of preventing paralysis, according to a study conducted by Clausen et al., in mouse models, salbutamol has been effective at restoring the force of a given muscle and stimulating the sodium-potassium ATPase protein (Clausen et al., 2011). While there

are other beta-2 agonists that interact with these pathways, the specific drugs and mechanisms of action are beyond the scope of this paper.

So far, the treatment options section of this paper has focused almost exclusively on pharmaceutical intervention. This is because a study conducted by Charles et al. surveyed one of the largest cohorts of HyperPP patients in a study. A section of the survey asked patients to report on their personal treatment regimens. Patients could choose to designate their regimens as “needs improvement”, “mostly controlled”, or “optimal” in the observed ability to mitigate their symptoms. Only 4.8% of the patients surveyed designated their treatment regimen as “optimal”, with 50.6% describing their treatment protocols as “needs improvement”. A distinct minority of patients who designated their treatment as “mostly controlled” reported that they were not taking medication to control their symptoms, though a majority of patients who chose “needs improvement” claimed not to be taking medication. Another part of the patients’ treatment regimen that was commonly reported was their dietary restrictions, which will be discussed in the next chapter (G. Charles et al., 2013).

CHAPTER FOUR

Metabolism of Dietary Potassium and Other Related Nutrients

The Metabolic Cycle of Potassium and The Effect of Other Nutrients

The most readily available treatment option for HyperPP is the intentional development of a diet plan that reduces the frequency and duration of a patient's symptoms. Ingestion of dietary potassium has, and will, result in a change in the serum concentration of potassium (Udensi & Tchounwou, 2017). Therefore, the most direct way to prevent attacks of HyperPP is to avoid eating foods with a high potassium content. Unfortunately, since potassium is an integral intracellular ion in living systems, foods derived from living tissue tend to contain potassium. It is important to note, though, that the potassium content of fruits and vegetables are typically higher than that of cereals and meat (Stone et al., 2016).

Upon ingestion, foods containing potassium are transported to the stomach via the esophagus. From there, they enter the small intestine, which is the primary site of potassium absorption. This process occurs predominately through passive transport (Agarwal et al., 1994) as a result of the concentration difference between the lumen of the small intestine and the blood. Potassium is also passively transported from the lumen to the bloodstream along with water, regardless of the presence of an electrochemical gradient. This proposed phenomenon, called "solvent drag", implies that water carries the potassium with it as it travels through channels, or pores, in the mucosal membrane. Solvent drag, if present, would dramatically increase the potassium absorption capabilities of the small intestine (Turnberg, 1971).

Once the potassium is in the bloodstream, it needs to be stored so that it will not cause metabolic imbalance while the body works to excrete the excess, to maintain homeostasis. Only about 2% of the total amount of potassium in the body exists in extracellular fluids. The serum potassium concentration for a normal individual should stay between 3.5mmol/L and 5.0mmol/L (Udensi & Tchounwou, 2017). Previous studies indicate that 4-6 hours after the ingestion of potassium, 50% is excreted by the kidneys in the urine (Youn, 2013), and 80% of what remains is distributed across various tissues (Bia & DeFronzo, 1981) such as the liver and skeletal muscles (Youn, 2013). In fact, physiologically normal skeletal muscle cells routinely act as a buffer system for potassium homeostasis (Palmer, 2015).

To maintain homeostasis after a meal, the small intestine has to recognize the potassium it is absorbing and alert the kidneys to increase potassium excretion. The precise mechanism of this signaling process is still unknown, but one proposal indicates that the signaling may occur result in the "rapid and nearly complete dephosphorylation of the [sodium-chloride] cotransporter in the [distal convoluted tubule]" of the kidney (Palmer, 2015). According to previous studies, the traditional view of this pathway employed negative feedback regulation. This proposal contends that an increase in the extracellular potassium concentration causes the release of aldosterone, which stimulates the kidneys to excrete more potassium in the urine, returning the levels of extracellular potassium to normal. More recently, another mechanism was proposed by Rabinowitz that employs feedforward control, but it is beyond the scope of this paper (Youn, 2013).

While there are alternate modes of excretion available, such as stool and sweat, 90% of dietary potassium is eliminated in the urine. In the kidney, potassium excretion is

regulated in the late distal convoluted tubule. The amount of potassium excreted is partially dependent on the movement of sodium ions. The sodium-chloride cotransporter permits the efflux of sodium ions from the lumen of the distal convoluted tubule into the peritubular capillary fluid. The reabsorption of sodium ions leads to the formation of an electrochemical gradient, where the lumen of the distal convoluted tubule is more negative than the peritubular capillary fluid. This causes the movement of potassium ions into the luminal fluid to alleviate the charge. The luminal fluid eventually becomes urine and the potassium is eliminated from the body (Stone et al., 2016).

The second factor that stimulates potassium excretion is the release of aldosterone, a mineralocorticoid hormone. Aldosterone acts on the nephron by two main mechanisms: the aldosterone-sensitive distal nephron and the renin-angiotensin-aldosterone system. The former is activated in response to the reabsorption of sodium and the secretion of potassium to alleviate hyperkalemia. Aldosterone opens more of the sodium channels in the collecting tubule, increasing the sodium reabsorption capabilities of the nephron. The latter is activated as a response to low blood volume in the distal convoluted tubule. When hyperkalemia is experienced, the renin-angiotensin-aldosterone system is capable of acting only on cells responsible for potassium secretion and stimulating them, specifically. This yields a decrease in serum potassium concentration without changing the concentration of sodium (Udensi & Tchounwou, 2017).

Now that the method of potassium excretion has been explained, another way in which serum potassium concentration fluctuates can be addressed. Potassium homeostasis is dependent upon adjustments made by tissues to either release or absorb extracellular potassium. This is accomplished by transport proteins such as the sodium-potassium

chloride symporter, sodium-calcium exchanger, and the sodium-potassium ATPase, which function to move ions across semipermeable membranes. If sodium-potassium ATPase proteins are stimulated by beta-2 agonists and insulin, the activity of the pump increases, permitting a more rapid influx of potassium. However, a decrease in the pH of the extracellular fluid decreases the activity of the sodium-potassium ATPase protein, which reduces the influx of potassium. In fact, through interactions with other proteins, decreased extracellular fluid actually causes the efflux of potassium (Stone et al., 2016).

Another factor that is integral in the maintenance of potassium homeostasis is the hormone insulin (Bia & DeFronzo, 1981). As previously mentioned, insulin activates the sodium-potassium ATPase pump, allowing the intracellular concentration of potassium to increase (Stone et al., 2016). According to some studies, the effects of insulin and catecholamines are "the most important factors in regulating [the] movement" of potassium between extracellular and intracellular spaces (Palmer, 2015). Though insulin is commonly associated with the influx of glucose, a study conducted by Nguyen et al. established that the mechanism by which insulin increases the influx of potassium is not related to the transport of glucose (Nguyen et al., 2011).

Insulin's ability to act as an activator of the sodium-potassium ATPase pump makes it very important in the treatment of HyperPP. One option for acute treatment, for use in the preventions of an imminent attack, is the ingestion of carbohydrates. Carbohydrates stimulate the release of insulin due to its effect on the transport of glucose into the cell (Geser, 1976). However, as discussed previously, insulin also effectively stimulates a reduction in the concentration of extracellular potassium. As mentioned in the last chapter, that process can mitigate the symptoms of HyperPP.

CHAPTER FIVE

Novel Management Tool Proposal

Potassium and Symptom Tracking Application for Patients with Hyperkalemic Periodic Paralysis

After reviewing the various treatment methods, the most readily available, efficacious option for the mitigation of symptoms is diet control. Regulating the intake of dietary potassium can be done autonomously and varied expediently. Most foods contain at least some potassium (Stone et al., 2016) and anecdotal evidence suggests that the amount is not always noted on nutrition labels. For this reason, among others, it would be prudent to assemble a central database to house dietary potassium content. Though nutrient data, including potassium information, is collected and contained in government and other nutritional databases, the sources are sporadic, and the validity of the data is unknown. An excellent way to collect this information and make it readily accessible by the HyperPP patient population would be to construct an application that could be downloaded and integrated into personal technology such as smart phones or laptops.

The first step to creating an application like this would be to compile the nutrient data from different sources, identify the most reliable data, and make arrangements with the companies which own the data to secure the rights to use it. Once a database is constructed, the coding that allows a database to be searched, a food item and amount to be selected, and the nutrient data added to a log must be completed. While references to coding will continue to appear throughout this chapter, the details of this process are outside of the scope of this paper.

Applications capable of simply tracking potassium data do currently exist; however, coupling this capability with the ability to track a patient's symptoms would differentiate this application and improve its efficacy for HyperPP patients. Since, as discussed throughout this paper, the symptom manifestation of HyperPP varies across the patient population, the list would need to be extensive. It would also be helpful to include an option for patients to add their own symptoms to their account to ensure that the application is as expansive as possible and able to accommodate their individual symptoms.

The "symptoms" page should be ergonomically designed to minimize the movements required to log a patient's symptoms since one of the hallmark symptoms of HyperPP is paralysis, which would limit complex interface with the application. This could be done by designing the page to display an outline of a person with division lines marking different regions of the body (see Appendix), one from an anterior view and one from a posterior view. The symptom list could be categorized by region, allowing patients to easily access area specific symptoms.

Symptoms could be logged by tapping the region of the body in which they are experienced and selecting specific symptoms from the dropdown menu that appears containing regional symptoms. It would be helpful if the application was able to remember recently logged symptoms and those experienced often by patients, and list those at the top to make logging them more convenient. Since patients can experience several symptoms at once, it is important to allow them to select several symptoms from the list for each region. Generalized, systemic symptoms can be added using the "generalized symptoms" button located at the bottom of the screen (see Appendix).

For this application to be effective, there are several considerations which must be addressed. First, patient metabolic rates are not standardized, so individuals will excrete potassium at different rates. One way to eliminate this problem would be to create a computer algorithm that is capable of assimilating the data input by the patient about the food they eat and the symptoms they experience and learning their potassium tolerance. Instead of associating the most recently logged food item with the most recently logged set of symptoms, this algorithm should be capable of associating the amount of potassium consumed in a given amount of time with the development of symptoms. This should reduce the need for provocative tests to establish a patient's potassium tolerance and reduce their risk of hyperkalemia, decreasing the likelihood that they experience symptoms of HyperPP.

As mentioned in previous chapters, nutrients other than potassium also have the potential to impact a patient's symptoms. The food database used by the application will include information regarding the nutritional content in individual food items, such as the amount of sodium, calcium, magnesium, and carbohydrates, and other pertinent nutrient information. This should allow the application to track several pieces of data at once, resulting in a more representative record of how nutrition impacts a patient.

In Chapter 3, potassium excretion mechanisms are discussed in detail. Since sweat and urine are, together, responsible for more than 90% of potassium excretion in a human (Stone et al., 2016), the application should also be able to keep a log of exercise, water intake, and urinary output. Although it may be inconvenient at first, logging urinary output volume would allow the application to more accurately estimate the amount of dietary potassium still present in the tissues. This would be an approximation given the lack of

home concentration testing capabilities, but as the technology improves, it may become more feasible. If the application can adjust its calculated estimate of a patient's potassium metabolic rate based on activity level, water intake, and urinary output volume, then it will be able to give a more accurate approximation of their current potassium tolerance.

With continued use, this application may be able to anticipate an attack based on a patient's food and water intake, activity level, and previous symptom manifestation patterns. Once that occurs, the application should be able to give recommendations in real time. For example, if a patient logs a meal that they are planning to consume, and the food they log increases their potassium level to a point that has caused symptoms in the past, the application will send them an alert and notify them of the possible ramifications of their decision. Real time feedback may help patients avoid high potassium foods, as well as inconvenient symptom manifestation.

Another helpful feature would be a "snack reminder" delivered through the application's notification center. Since patients who experience HyperPP should refrain from fasting to decrease the frequency of their symptoms (V. Sansone et al., 2008), a reminder to eat could be very helpful. To make this feature even more beneficial, a "quick snacks" page could be constructed. This page would generate a list of frequently eaten snacks that are within a patient's current potassium tolerance. This list would update in real time, allowing patients to make more informed decisions regarding their nutrition.

If the application is capable of anticipating attacks, it may be able to learn how to reverse them. After dedicated use, the algorithm may be capable of discerning which reversal mechanism would be the most effective based on a patient's symptoms and nutrition decisions. Including a "reversal options" page that could track the efficiency and

effectiveness of different reversal attempts would allow patients to find the appropriate treatment quickly. To do this, patients would have to attempt the potential reversal method, when an attack happens. After the attack is over, they would need to rate the reversal in terms of metrics, such as: how long it took to produce an effect, the method's ability to reduce the intensity of the symptoms, and how long the attack lasted. The algorithm should eventually gain enough information to recommend treatment based on the patient's projected potassium tolerance.

Beyond acute symptom mitigation, this application could have broader medical implications. A "general information" page that summarized the cause, diagnostic criteria, and typical symptoms of HyperPP would give patients knowledge about their condition that would allow them to ask their medical provider questions about their healthcare and future. Also, it would give patients a resource to explain the condition to those around them to foster productive conversations with their family and friends. Also, some of the symptoms may be unnerving, so understanding why they happen may help patient mental health.

Another medical consideration is patient response to prescribed medication. In Chapter 2, medications, and the mechanisms by which they effect patients, are discussed in detail. Different classes of drugs result in varying physiological changes, which will in turn change how patients with HyperPP experience symptoms, based on the individual. This proposed application could provide patients with valuable data about how the drugs they take might affect them. By logging the medication they take, patients then have a record of what time they took the medication and the symptoms they experienced in that timeframe. This could assist physicians in finding the appropriate medication for their

patient more quickly because they would be able to review the patient's response in a sequential, time-stamped spreadsheet instead of relying on the speculative recall of the patient.

To ensure optimal patient care in an emergency situation, patients with HyperPP need to be able to notify the medical team of their condition. However, in such situations in which the patient is fully paralyzed and cannot speak, or is unconscious, this is impossible. This application can alleviate that concern by integrating into the patient's emergency page found on their smart phone. This page could contain medications that they cannot tolerate, anesthesia considerations, general information about HyperPP, along with their weight, list of comorbidities, and their primary care physician's name and office number. Having ready access to this information could help emergency medical teams to provide the patient with safe, rapid treatment.

When the application is downloaded and a login is created for the patient, there will be a process required to set up the application to individual specifications. First, while they are feeling well, patients will be asked to select the symptoms they feel when they experience an attack from the database of symptoms included in the application. This will customize their symptoms page by listing their commonly experienced symptoms at the top of the regional symptoms list, allowing them to quickly select the appropriate symptoms while minimizing the movement it takes to do so. Secondly, patients will have the option to set up their emergency page and be presented with an explanation as to why it may be beneficial. The next step in setting up the application will give patients the opportunity to designate a "community" within the application. This will permit patients to input family members or friends from their contacts list into the application's notification

center. If they choose to utilize this function, they will have the opportunity to type a message that requests non-emergent help from their "community" members. If this function is enabled, when a patient begins to develop symptoms, they can select the "community button" and choose a contact to which their pretyped message will be sent. The final feature that will need to be addressed as the application is installed is the Global Positioning System (GPS). This application may have the ability to utilize the personal technology's GPS system to notify the patient's "community" of their location when a request non-emergent help is sent. Of course, this function is optional, and patients will be notified of privacy considerations.

Due to the nature of the information that this application would contain, Health Insurance Portability and Accountability Act (HIPAA) compliance is essential for public use. The technical and legal implications of that requirement are beyond the scope of this paper, but because the application contains healthcare information, it would be prudent to determine the necessary steps in fulfilling HIPAA compliance.

This application will only work if it is utilized extensively, and the information it generates should never supersede a doctor's advice. It is simply a tool for patients who are attempting to mitigate their symptoms to a greater extent by observing their responses to nutrition decisions. Also, is designed to assist physicians in reviewing their patient's symptoms and dietary decisions so that they can make more informed diagnoses, suggest more effective treatment options, and have access to more accurate data. If this application is not used as it was intended, it will not be able to generate the data required to benefit the patients who use it; however, if it is used properly, it may provide patients with some degree of relief.

CHAPTER SIX

Conclusion

Plan to Determine the Efficacy of The Proposed Management Tool

Now that the disease is understood and a proposal has been discussed, it is important to elucidate why an application is needed. Being able to participate in their own healthcare solution gives patients who are frequently unable to control their muscles some control over the trajectory of their lives. When participating in a study, patients with HyperPP were asked to give advice to others who have the disease. One patient responded by stating that people with HyperPP need to "talk with others, learn how to manage your diet. You can take control of many things, even though mid-attack you have little to no control…Don't put things off, because you never know when the next big attack might come. We already must suffer being paralyzed physically, so let's not be paralyzed by fear, as well" (Grace Charles et al., n.d.). This response, and others like it, demonstrate the need for patients to control some aspect of their healthcare, and diet management is the easiest and safest way to give them that ability. The application proposed in this paper could provide a safe framework to allow patients the autonomy they need to feel better without compromising their health.

Patient surveys were completed in a 2013 study, conducted by Charles et al., to evaluate the HyperPP patient population. The study was comprised of 94 patients, with varying levels of responsiveness for individual questions. However, patients reported that, on average, it took them 19.4 years and four healthcare professionals from the first experienced symptoms to receive the correct diagnosis. For some patients, it took up to 10

healthcare professionals to receive the correct diagnosis. In this study, patients reported that they were commonly misdiagnosed with psychiatric disorders or accused of malingering before being diagnosed with HyperPP (G. Charles et al., 2013). One patient who had received their diagnosis responded to the survey warning others to "expect that most doctors you see are not going to believe you. But it is real, there are many people who have it and it can be managed" (Grace Charles et al., n.d.). Unfortunately, of the patients who responded to the survey, only 4.8% considered their symptoms to be managed to an "optimal" level. 50.6% of patients reported that their treatment protocols "needs improvement", while 44.6% claimed that their treatment protocols "mostly controlled" their symptoms. The most surprising response was that, despite the high percentage of patients that indicated their symptoms were "mostly controlled", 36 % of the patients surveyed were "never or are only occasionally able to abort an attack" and 48% of patients reported that their treatment protocol took them over 10 years to establish (G. Charles et al., 2013).

The aim of this paper is to provide something to help patients manage their symptoms while they wait to find a physician to help them, help patients establish a reasonable management plan, and augment the efficacy of the treatment prescribed or recommended by their physician. An application can be expected to be an especially effective platform to have the aforementioned affect because of the age group primarily afflicted with HyperPP. Most people develop symptoms in their early childhood and are most affected by the disease in their childhood and early adulthood (G. Charles et al., 2013). This early stage would be the period in which management techniques would likely be the most critical and the symptoms would be the most prevalent. Developing an

application would allow younger individuals, who would likely be familiar with and have access to technology, to establish a diet plan on a platform that they are already comfortable using.

To determine the success of this proposal, a study must be completed after the development of the application. First, exclusion criteria must be set to establish an appropriate patient population. Due to the possible complications of using a minor such as inconsistent reporting, parental discomfort with the procedure, and the novelty of the procedure, it would be best to limit the study to individuals over the age of majority. It also would be prudent to limit the study to genetically diagnosed individuals to ensure that the sample is, in fact, made up of patients with HyperPP. Finally, it should be established at the beginning of the study that patients whose data is inconsistently reported will be excluded to prevent the results from being skewed.

Before beginning the study, the researchers must obtain Institutional Review Board (IRB) approval and obtain informed consent from each subject in the study. Then, subject can complete a questionnaire, indicating the intensity and frequency of their symptoms, information about their current treatment protocols, general information about their health, and symptom history. The information collected from this questionnaire will be used as the control data for the study.

Subjects will be given login data for the application and instructed in its use. With the permission of the subjects, the data collected in the trial will be uploaded to a secure server as it is recorded to ensure that personal technical difficulties do not disrupt the study. The application will be tested over the course of 12 months. During the trial, patients will be asked to see their physician at least once every six months to ensure that their health is

being maintained at optimal levels. Subjects whose health declines while in the study will be excluded and the cause of their health problem will be ascertained and noted. If this pattern continues among other subjects, the study will be stopped and the application will be reevaluated.

At the end of the 12 month period, the subjects will be asked to complete a second questionnaire, which will have two parts. The first section will be identical to the pre-study questionnaire, while the second section will include an evaluation of the application. In this second part, patients will have the opportunity to discuss the efficiency of the application, how they feel about the display, and how likely they are to continue using it after the study is over. Inclusion of patient data in the study will be contingent on their completion of the post-study survey.

Patient responses will be paired with their control data and the efficacy of the application will be determined. If It is not performing optimally, the cause will be determined and addressed. After it has been redesigned to accommodate the problem, another study will be completed to reevaluate the effect of the change. Once it has been demonstrated to improve the ability of patients to control their symptoms, it will be released for public use.

APPENDIX

Symptom Page Illustration

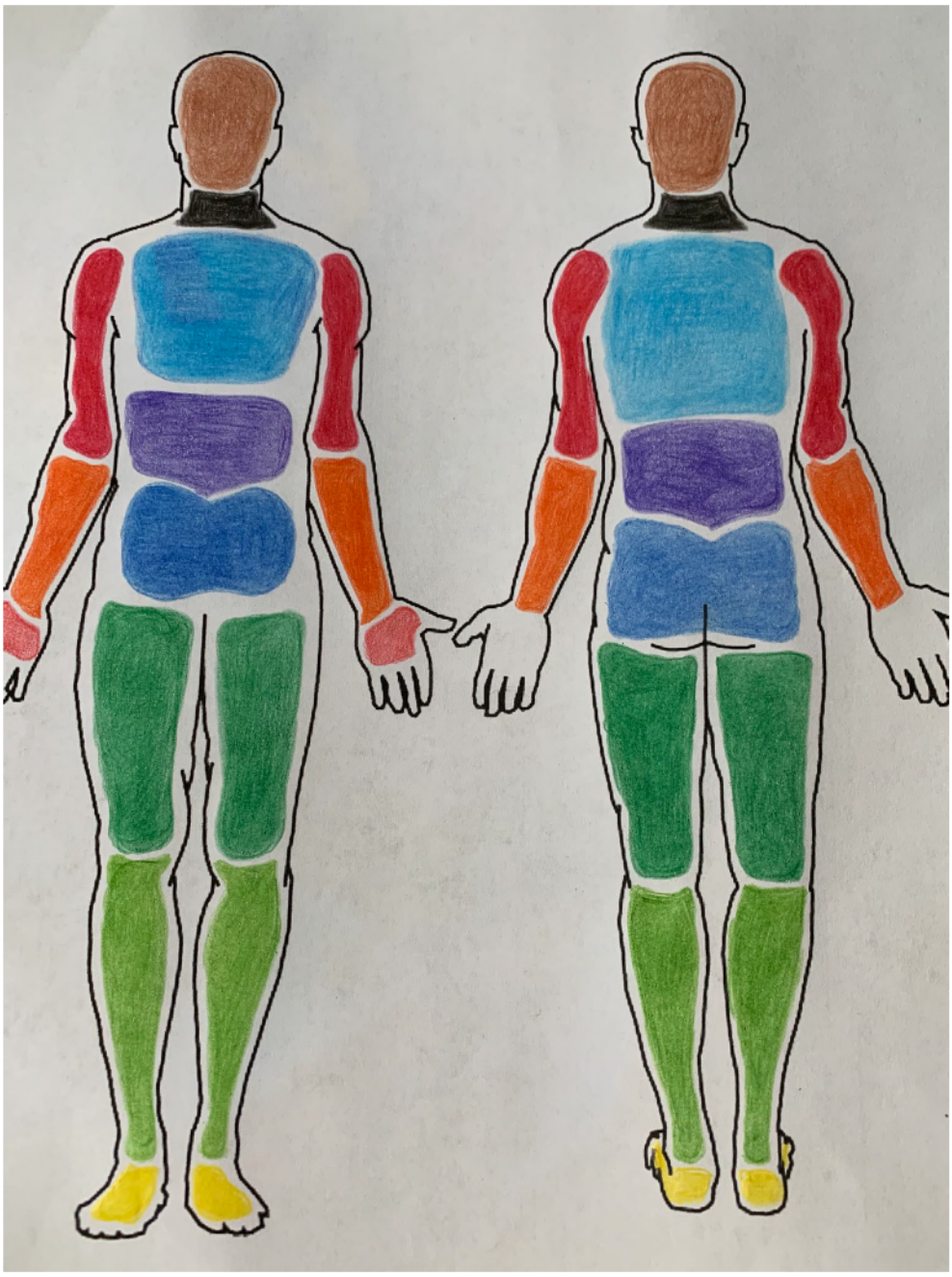

Image Outline Source: ("12+ Human Body Outline Templates (in Word & PDF) - Doc Formats," 2019)

BIBLIOGRAPHY

Agarwal, R., R. Afzalpurkar, and J. S. Fordtran. "Pathophysiology of Potassium Absorption and Secretion by the Human Intestine." *Gastroenterology* 107, no. 2 (August 1994): 548–71. https://doi.org/10.1016/0016-5085(94)90184-8.

Akinrodoye, Micky A., and Forshing Lui. "Neuroanatomy, Somatic Nervous System." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK556027/.

Amarteifio, Erick, Armin M. Nagel, Marc-André Weber, Karin Jurkat-Rott, and Frank Lehmann-Horn. "Hyperkalemic Periodic Paralysis and Permanent Weakness: 3-T MR Imaging Depicts Intracellular 23Na Overload—Initial Results." *Radiology* 264, no. 1 (July 1, 2012): 154–63. (Ueda et al., 2019).

Ammar, Tarek, Wei Lin, Amanda Higgins, Lawrence J. Hayward, and Jean-Marc Renaud. "Understanding the Physiology of the Asymptomatic Diaphragm of the M1592V Hyperkalemic Periodic Paralysis Mouse." *Journal of General Physiology* 146, no. 6 (December 1, 2015): 509–25. https://doi.org/10.1085/jgp.201511476.

Arrowsmith, Joseph E. "The Neuromuscular Junction." *Surgery (Oxford)*, Critical Illness and intensive care, 25, no. 3 (March 1, 2007): 105–11. https://doi.org/10.1016/j.mpsur.2007.02.001.

Bankenahally, R., and H. Krovvidi. "Autonomic Nervous System: Anatomy, Physiology, and Relevance in Anaesthesia and Critical Care Medicine." *BJA Education* 16, no. 11 (November 1, 2016): 381–87. https://doi.org/10.1093/bjaed/mkw011.

Benarroch, Eduardo E. "THE AUTONOMIC NERVOUS SYSTEM: BASIC ANATOMY AND PHYSIOLOGY." *CONTINUUM: Lifelong Learning in Neurology* 13 (December 2007): 13–32. https://doi.org/10.1212/01.CON.0000299964.20642.9a.

Bia, M. J., and R. A. DeFronzo. "Extrarenal Potassium Homeostasis." *The American Journal of Physiology* 240, no. 4 (April 1981): F257-268. https://doi.org/10.1152/ajprenal.1981.240.4.F257.

Braithwaite, Johann P., and Yasir Al Khalili. "Physiology, Muscle Myocyte." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK544225/.

Burdusel C. “Basic Facts about Neurons.” *Australasian Journal of Neuroscience* 17, no. 2 (January 2006): 9–12.

Burge, James, Valeria Sansone, Michael McDermott, Patty Smith, Barbara Herr, Alrabi Tawil, Shree Pandya, et al. “Efficacy and Safety of Dichlorphenamide for the Treatment of Periodic Paralysis: A Phase 3 Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial (PL02.001).” *Neurology* 86, no. 16 Supplement (April 5, 2016). https://n.neurology.org/content/86/16_Supplement/PL02.001.

Cannon, Stephen C. “Channelopathies of Skeletal Muscle Excitability.” *Comprehensive Physiology* 5, no. 2 (April 2015): 761–90. https://doi.org/10.1002/cphy.c140062.

Catterall, William A. “Voltage-Gated Sodium Channels at 60: Structure, Function and Pathophysiology.” *The Journal of Physiology* 590, no. Pt 11 (June 1, 2012): 2577–89. https://doi.org/10.1113/jphysiol.2011.224204.

Charles, G., C. Zheng, F. Lehmann-Horn, K. Jurkat-Rott, and J. Levitt. “Characterization of Hyperkalemic Periodic Paralysis: A Survey of Genetically Diagnosed Individuals.” *Journal of Neurology* 260, no. 10 (2013): 2606–13. https://doi.org/10.1007/s00415-013-7025-9.

Charles, Grace, Chengjie Zheng, and Jacob Levitt. “Hyperkalemic Periodic Paralysis,” n.d., 34.

Clausen, Torben, Ole Bækgaard Nielsen, Johannes D. Clausen, Thomas Holm Pedersen, and Lawrence J. Hayward. “Na+,K+-Pump Stimulation Improves Contractility in Isolated Muscles of Mice with Hyperkalemic Periodic Paralysis.” *Journal of General Physiology* 138, no. 1 (July 1, 2011): 117–30. https://doi.org/10.1085/jgp.201010586.

Clausen, Torben, Palle Wang, Hans Ørskov, and Ole Kristensen. “Hyperkalemic Periodic Paralysis. Relationships between Changes in Plasma Water, Electrolytes, Insulin and Catecholamines during Attacks.” *Scandinavian Journal of Clinical and Laboratory Investigation* 40, no. 3 (January 1, 1980): 211–20. https://doi.org/10.3109/00365518009095569.

Document Formats. “12+ Human Body Outline Templates (in Word & PDF) - Doc Formats,” November 12, 2019. https://www.docformats.com/12-body-outline-templates/.

Ellison, David H., Andrew S. Terker, and Gerardo Gamba. “Potassium and Its Discontents: New Insight, New Treatments.” *Journal of the American Society of Nephrology : JASN* 27, no. 4 (April 2016): 981–89. https://doi.org/10.1681/ASN.2015070751.

Fontaine, B, T. Khurana, E. Hoffman, G. Bruns, J. Haines, J. Trofatter, M. Hanson, et al. "Hyperkalemic Periodic Paralysis and the Adult Muscle Sodium Channel Alpha-Subunit Gene." *Science* 250, no. 4983 (November 16, 1990): 1000–1002. https://doi.org/10.1126/science.2173143.

Fontaine, Bertrand, Pascale Lapie, Emmanuelle Plassart, Nacira Tabti, Sophie Nicole, Jocelyne Reboul, and Claire-Sophie Rime-Davoine. "Periodic Paralysis and Voltage-Gated Ion Channels." *Kidney International* 49, no. 1 (January 1996): 9–18. https://doi.org/10.1038/ki.1996.2.

George, A. L., G. S. Iyer, R. Kleinfield, R. G. Kallen, and R. L. Barchi. "Genomic Organization of the Human Skeletal Muscle Sodium Channel Gene." *Genomics* 15, no. 3 (March 1993): 598–606. https://doi.org/10.1006/geno.1993.1113.

Geser, C. A. "Hormonal Interactions in Carbohydrate Metabolism." *Internationale Zeitschrift Fur Vitamin- Und Ernahrungsforschung. Beiheft* 15 (1976): 58–65.

Green, Donnella S, Alfred L George, and Stephen C Cannon. "Human Sodium Channel Gating Defects Caused by Missense Mutations in S6 Segments Associated with Myotonia: S804F and V1293I." *The Journal of Physiology* 510, no. Pt 3 (August 1, 1998): 685–94. https://doi.org/10.1111/j.1469-7793.1998.685bj.x.

Greig, Sarah L. "Dichlorphenamide: A Review in Primary Periodic Paralyses." *Drugs* 76, no. 4 (March 2016): 501–7. https://doi.org/10.1007/s40265-016-0559-2.

Grider, Michael H., and Carolyn S. Glaubensklee. "Physiology, Action Potential." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK538143/.

Hayward, L J, R H Brown, and S C Cannon. "Slow Inactivation Differs among Mutant Na Channels Associated with Myotonia and Periodic Paralysis." *Biophysical Journal* 72, no. 3 (March 1997): 1204–19.

Hehir, Michael K., and Eric L. Logigian. "Electrodiagnosis of Myotonic Disorders." *Physical Medicine and Rehabilitation Clinics of North America* 24, no. 1 (February 2013): 209–20. https://doi.org/10.1016/j.pmr.2012.08.015.

Herman, Linda L., and Khalid Bashir. "Hydrochlorothiazide." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK430766/.

Huxel, Chris, Avais Raja, and Michelle D. Ollivierre-Lawrence. "Loop Diuretics." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK546656/.

Iaizzo, Paul A., Stefan Quasthoff, and Frank Lehmann-Horn. "Differential Diagnosis of Periodic Paralysis Aided by in Vitro Myography." *Neuromuscular Disorders* 5, no. 2 (March 1, 1995): 115–24. https://doi.org/10.1016/0960-8966(94)00036-9.

Johnson, Nicholas, Jeffrey Statland, Fredric Cohen, and Robert Griggs. "Long-Term Efficacy of Dichlorphenamide for the Treatment of Primary Periodic Paralysis (PPP) (P5.4-008)." *Neurology* 92, no. 15 Supplement (April 9, 2019). https://n.neurology.org/content/92/15_Supplement/P5.4-008.

Jurkat-Rott, Karin, Boris Holzherr, Michael Fauler, and Frank Lehmann-Horn. "Sodium Channelopathies of Skeletal Muscle Result from Gain or Loss of Function." *Pflugers Archiv* 460, no. 2 (July 2010): 239–48. https://doi.org/10.1007/s00424-010-0814-4.

Jurkat-Rott, Karin, and Frank Lehmann-Horn. "Genotype-Phenotype Correlation and Therapeutic Rationale in Hyperkalemic Periodic Paralysis." *Neurotherapeutics* 4, no. 2 (April 1, 2007): 216–24. https://doi.org/10.1016/j.nurt.2007.02.001.

Kameneva, Polina, and Igor Adameyko. "Recent Advances in Our Understanding of Central and Peripheral Nervous System Progenitors." *Current Opinion in Cell Biology* 61 (December 2019): 24–30. https://doi.org/10.1016/j.ceb.2019.07.003.

Khogali, Shiemaa, Brooke Lucas, Tarek Ammar, Danica Dejong, Michael Barbalinardo, Lawrence J. Hayward, and Jean-Marc Renaud. "Physiological Basis for Muscle Stiffness and Weakness in a Knock-in M1592V Mouse Model of Hyperkalemic Periodic Paralysis." *Physiological Reports* 3, no. 12 (2015): e12656. https://doi.org/10.14814/phy2.12656.

Kim, June-Bum. "Channelopathies." *Korean Journal of Pediatrics* 57, no. 1 (January 2014): 1–18. https://doi.org/10.3345/kjp.2014.57.1.1.

Kullmann, Dimitri M, and Michael G Hanna. "Neurological Disorders Caused by Inherited Ion-Channel Mutations." *The Lancet Neurology* 1, no. 3 (July 2002): 157–66. https://doi.org/10.1016/S1474-4422(02)00071-6.

Lehmann -Horn, F., P. A. Iaizzo, H. Hatt, and Ch. Franke. "Altered Gating and Conductance of Na+ Channels in Hyperkalemic Periodic Paralysis." *Pflügers Archiv* 418, no. 3 (April 1, 1991): 297–99. https://doi.org/10.1007/BF00370530.

Lehmann-Horn, Frank, and Karin Jurkat-Rott. "Voltage-Gated Ion Channels and Hereditary Disease." *Physiological Reviews* 79, no. 4 (January 10, 1999): 1317–72. https://doi.org/10.1152/physrev.1999.79.4.1317.

Lodish, Harvey, Arnold Berk, S. Lawrence Zipursky, Paul Matsudaira, David Baltimore, and James Darnell. "The Action Potential and Conduction of Electric Impulses."

Molecular Cell Biology. 4th Edition, 2000. https://www.ncbi.nlm.nih.gov/books/NBK21668/.

Mahadevan, Vishy. "Neuroanatomy: An Overview." *Surgery (Oxford)* 36, no. 11 (November 1, 2018): 597–605. https://doi.org/10.1016/j.mpsur.2018.09.010.

Matthews, E., and M. G. Hanna. "Repurposing of Sodium Channel Antagonists as Potential New Anti-Myotonic Drugs." *Experimental Neurology* 261 (November 1, 2014): 812–15. https://doi.org/10.1016/j.expneurol.2014.09.003.

McCuller, Christopher, Rishita Jessu, and Avery L. Callahan. "Physiology, Skeletal Muscle." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK537139/.

OpenStax. "12.1 Basic Structure and Function of the Nervous System." In *Anatomy and Physiology*. OpenStax, 2013. https://opentextbc.ca/anatomyandphysiology/chapter/12-1-basic-structure-and-function-of-the-nervous-system/.

OpenStax. "12.4 The Action Potential." In *Anatomy and Physiology*. OpenStax, 2013. https://opentextbc.ca/anatomyandphysiology/chapter/12-4-the-action-potential/.

"Neuromuscular: Fiber Activity." Accessed May 18, 2020. https://neuromuscular.wustl.edu/mother/activity.html#hrpp.

Nguyen, Trang Q., Naim M. Maalouf, Khashayar Sakhaee, and Orson W. Moe. "Comparison of Insulin Action on Glucose versus Potassium Uptake in Humans." *Clinical Journal of the American Society of Nephrology* 6, no. 7 (July 1, 2011): 1533–39. https://doi.org/10.2215/CJN.00750111.

Nikolić, A. "3. Electrophysiologic Diagnostics of Myotonia." *Clinical Neurophysiology* 124, no. 7 (July 2013): e9. https://doi.org/10.1016/j.clinph.2012.12.012.

Palmer, Biff F. "Regulation of Potassium Homeostasis." *Clinical Journal of the American Society of Nephrology : CJASN* 10, no. 6 (June 5, 2015): 1050–60. https://doi.org/10.2215/CJN.08580813.

Pan, Xiaojing, Zhangqiang Li, Qiang Zhou, Huaizong Shen, Kun Wu, Xiaoshuang Huang, Jiaofeng Chen, et al. "Structure of the Human Voltage-Gated Sodium Channel Nav1.4 in Complex with B1." *Science* 362, no. 6412 (October 19, 2018). https://doi.org/10.1126/science.aau2486.

Plassart, Emmanuelle, Jocelyne Reboul, Claire-Sophie Rime, Dominique Recan, Philippe Millasseau, Bruno Eymard, Jean Pelletier, et al. "Mutations in the Muscle Sodium Channel Gene (SCN4A) in 13 French Families with Hyperkalemic Periodic Paralysis and Paramyotonia Congenita: Phenotype to Genotype Correlations and

Demonstration of the Predominance of Two Mutations." *European Journal of Human Genetics* 2, no. 2 (April 1994): 110–24. https://doi.org/10.1159/000472351.

Rinomhota AS, and Cooper K. "Clinical. Homeostasis: Restoring the Internal Wellbeing in Patients/Clients." *British Journal of Nursing* 5, no. 18 (October 10, 1996): 1100–1108.

Ruff, R L. "Slow Na+ Channel Inactivation Must Be Disrupted to Evoke Prolonged Depolarization-Induced Paralysis." *Biophysical Journal* 66, no. 2 Pt 1 (February 1994): 542–45.

Sansone, Valeria A., James Burge, Michael P. McDermott, Patty C. Smith, Barbara Herr, Rabi Tawil, Shree Pandya, et al. "Randomized, Placebo-Controlled Trials of Dichlorphenamide in Periodic Paralysis." *Neurology* 86, no. 15 (April 12, 2016): 1408–16. https://doi.org/10.1212/WNL.0000000000002416.

Sansone, Valeria, Giovanni Meola, Thera Links, Marta Panzeri, and Michael R. Rose. "Treatment for Periodic Paralysis." *Cochrane Database of Systematic Reviews*, no. 1 (2008). https://doi.org/10.1002/14651858.CD005045.pub2.

Sasaki, Ryogen, Hiroki Takano, Keiko Kamakura, Kenichi Kaida, Akira Hirata, Masaaki Saito, Hajime Tanaka, Shigeki Kuzuhara, and Shoji Tsuji. "A Novel Mutation in the Gene for the Adult Skeletal Muscle Sodium Channel α-Subunit (SCN4A) That Causes Paramyotonia Congenita of von Eulenburg." *Archives of Neurology* 56, no. 6 (June 1, 1999): 692–96. https://doi.org/10.1001/archneur.56.6.692.

Shrimanker, Isha, and Sandeep Bhattarai. "Electrolytes." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK541123/.

Simkin, Dina, and Saïd Bendahhou. "Skeletal Muscle Na+ Channel Disorders." *Frontiers in Pharmacology* 2 (October 14, 2011). https://doi.org/10.3389/fphar.2011.00063.

Singh, Shashank, Connor C. Kerndt, and Roman Zeltser. "Mexiletine." In *StatPearls*. Treasure Island (FL): StatPearls Publishing, 2020. http://www.ncbi.nlm.nih.gov/books/NBK519045/.

"SCN4A - Sodium Channel Protein Type 4 Subunit Alpha - Homo Sapiens (Human) - SCN4A Gene & Protein." Accessed May 18, 2020. https://www.uniprot.org/uniprot/P35499.

Statland, Jeffrey M., and Richard J. Barohn. "Muscle Channelopathies: The Nondystrophic Myotonias and Periodic Paralyses." *Continuum : Lifelong Learning in Neurology* 19, no. 6 Muscle Disease (December 2013): 1598–1614. https://doi.org/10.1212/01.CON.0000440661.49298.c8.

Statland, Jeffrey M., Bertrand Fontaine, Michael G. Hanna, Nicholas E. Johnson, John T. Kissel, Valeria A. Sansone, Perry B. Shieh, et al. "Review of the Diagnosis and Treatment of Periodic Paralysis." *Muscle & Nerve* 57, no. 4 (April 2018): 522–30. https://doi.org/10.1002/mus.26009.

Stino, Amro, and Stanley Iyadurai. "Cold-Induced Decrement and Electrical Myotonia in a Family with DNM2 Mutation without Clinical Myotonia (P3.115)." *Neurology* 88, no. 16 Supplement (April 18, 2017). https://n.neurology.org/content/88/16_Supplement/P3.115.

Stone, Michael S., Lisa Martyn, and Connie M. Weaver. "Potassium Intake, Bioavailability, Hypertension, and Glucose Control." *Nutrients* 8, no. 7 (July 22, 2016). (Agarwal et al., 1994).

Takahashi, Masanori P., and Stephen C. Cannon. "Enhanced Slow Inactivation by V445M: A Sodium Channel Mutation Associated with Myotonia." *Biophysical Journal* 76, no. 2 (February 1, 1999): 861–68. https://doi.org/10.1016/S0006-3495(99)77249-8.

Tan, S. Veronica, Karen Suetterlin, Roope Männikkö, Emma Matthews, Michael G. Hanna, and Hugh Bostock. "In Vivo Assessment of Interictal Sarcolemmal Membrane Properties in Hypokalaemic and Hyperkalaemic Periodic Paralysis." *Clinical Neurophysiology* 131, no. 4 (April 1, 2020): 816–27. https://doi.org/10.1016/j.clinph.2019.12.414.

Turnberg, L. A. "Potassium Transport in the Human Small Bowel." *Gut* 12, no. 10 (October 1971): 811–18. https://doi.org/10.1136/gut.12.10.811.

Udensi, Udensi K., and Paul B. Tchounwou. "Potassium Homeostasis, Oxidative Stress, and Human Disease." *International Journal of Clinical and Experimental Physiology* 4, no. 3 (2017): 111–22. https://doi.org/10.4103/ijcep.ijcep_43_17.

Ueda, Yuichiro, Susumu Ookawara, Haruhisa Miyazawa, Kiyonori Ito, Keiji Hirai, Taro Hoshino, Yoshiyuki Morishita, et al. "Changes in Serum and Urinary Potassium Handling Associated with Renin-Angiotensin-Aldosterone System Inhibitors in Advanced Chronic Kidney Disease Patients." *Cureus Journal of Medical Science* 11, no. 9 (September 4, 2019). https://doi.org/10.7759/cureus.5561.

Vardanyan, Ruben, and Victor Hruby. "Chapter 21 - Diuretics." In *Synthesis of Best-Seller Drugs*, edited by Ruben Vardanyan and Victor Hruby, 317–27. Boston: Academic Press, 2016. https://doi.org/10.1016/B978-0-12-411492-0.00021-3.

Venance, S. L., S. C. Cannon, D. Fialho, B. Fontaine, M. G. Hanna, L. J. Ptacek, M. Tristani-Firouzi, R. Tawil, R. C. Griggs, and CINCH investigators. "The Primary Periodic Paralyses: Diagnosis, Pathogenesis and Treatment." *Brain: A Journal of*

Neurology 129, no. Pt 1 (January 2006): 8–17. https://doi.org/10.1093/brain/awh639.

Weber, Frank, Karin Jurkat-Rott, and Frank Lehmann-Horn. "Hyperkalemic Periodic Paralysis." In *GeneReviews*®, edited by Margaret P. Adam, Holly H. Ardinger, Roberta A. Pagon, Stephanie E. Wallace, Lora JH Bean, Karen Stephens, and Anne Amemiya. Seattle (WA): University of Washington, Seattle, 1993. http://www.ncbi.nlm.nih.gov/books/NBK1496/.

Weckbecker, K., A. Würz, B. Mohammadi, T. Mansuroglu, A. L. George Jr, H. Lerche, R. Dengler, F. Lehmann-Horn, and N. Mitrovic. "Different Effects of Mexiletine on Two Mutant Sodium Channels Causing Paramyotonia Congenita and Hyperkalemic Periodic Paralysis." *Neuromuscular Disorders* 10, no. 1 (January 1, 2000): 31–39. https://doi.org/10.1016/S0960-8966(99)00060-7.

Whyte, K F, G J Addis, R Whitesmith, and J L Reid. "The Mechanism of Salbutamol-Induced Hypokalaemia." *British Journal of Clinical Pharmacology* 23, no. 1 (January 1987): 65–71.

Youn, Jang H. "Gut Sensing of Potassium Intake and Its Role in Potassium Homeostasis." *Seminars in Nephrology* 33, no. 3 (May 2013): 248–56. https://doi.org/10.1016/j.semnephrol.2013.04.005.